Afr. J. Med. Med. Sci. (2021) **50,** 357-364

Estimating the admission lifetime and survival for gynaecological cancers at the University College Hospital, Ibadan using cox regression model

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Abstract
Objective: To estimate the admission lifetime of gynaecological cancer patients in the University College Hospital (UCH), Ibadan and its implication to management and overall outcome using the Cox regression model.
Methods: Descriptive and cox regression model in survival analysis were used to analyze data from 823 patients with gynaecological malignancies who were treated at the UCH, Ibadan between January 1 1995 and December 31, 2014. The outcome variable for this study was the admission life-time (in days). The variables collected were limited to the age of patients, types of cancer and patients' status. The study employed some model criteria such as p-value, log rank test, Gehan-Wilcoxon test, Concordance index, R-square, likelihood ratio test, Wald test and score test to check for the efficiency of the results.
Results: Of the 823 cases reviewed, 611(74.2%) were right-censored. Cervical cancer had the highest number of patients admitted with 53.5% and was commonest among patients aged 60 years and above (30.1%) while mortality was highest among patients with ovarian cancer. Ovarian cancer and age above 65 years were the only two factors that significantly affected patient's survival experiences during their admission at the hospital.
Conclusion: Patients younger than 60 years and with other gynecologic cancers, except ovarian, had better chances of survival over a period of 6 months as at the time of admission into the UCH, Ibadan.

Keywords: *Cervical cancer, Cox regression model, Gynaecological cancers, Survival Analysis*.

Résumé
Objectif : Estimer la durée de vie de l'admission des patientes atteintes d'un cancer gynécologique à l'University College Hospital (UCH) d'Ibadan et son implication dans la gestion et les résultats globaux à l'aide du modèle de régression de Cox.
Méthodes : Un modèle de régression descriptif et de Cox dans l'analyse de survie a été utilisé pour analyser les données de 823 patientes atteintes de tumeurs malignes gynécologiques qui ont été traitées à l'UCH, Ibadan entre le 1er janvier 1995 et le 31 décembre 2014. La variable de résultat pour cette étude était la durée d'admission à vie. temps (en jours). Les variables collectées se limitent à l'âge des patients, aux types de cancer et au statut des patients. L'étude a utilisé certains critères de modèle tels que la valeur p, le test du log rank, le test de Gehan-Wilcoxon, l'indice de concordance, le R carré, le test du rapport de vraisemblance, le test de Wald et le test de score pour vérifier l'efficacité du résultat.
Résultats : Sur les 823 cas examinés, 611 (74,2 %) étaient censurés à droite. Le cancer du col de l'utérus comptait le plus grand nombre de patientes admises avec 53,5% et était le plus fréquent chez les patientes âgées de 60 ans et plus (30,1%) tandis que la mortalité était plus élevée chez les patientes atteintes d'un cancer de l'ovaire. Le cancer de l'ovaire et l'âge supérieur à 65 ans étaient les deux seuls facteurs qui affectaient de manière significative les expériences de survie des patientes lors de leur admission à l'hôpital.
Conclusion : Les patientes de moins de 60 ans et atteintes d'autres cancers gynécologiques, hors ovaire, avaient des chances de survie lettre sur une période de 6 mois comme au moment de l'admission à l'UCH d'Ibadan.

Mots clés : *Cancer du col de l'utérus, modèle de régression de Cox, cancers gynécologiques, analyse de survie.*

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Introduction

The medical needs of patients with cancers have undergone significant changes which are yet to be matched by commensurate changes in the delivery of healthcare services especially in low- and middle-income countries (LMICs) [1]. Gynaecological cancers are currently being noted to have become unrestricted to the elderly population with corresponding acute symptoms often requiring diverse interventions including being admitted for resuscitation, stabilization and/or optimization of clinical status in preparation for definitive management [1, 2]. This takes place across cancer types and it has been reported that hospital use hardly indicates an inappropriately aggressive care but rather serve an inevitable role in the trajectory of cancer care and management [2–5]. In addition, the severity of side effects of therapies for some specific cancers such as chemotherapy and radiotherapy often warrant repeated visits to the emergency departments with the frequency and duration of such admissions often contributing to the eventual outcome of care [3–6].

Admission life-time, otherwise refered to as patients' length of stay, (LOS), describes the total number of days a patient stays in the hospital while on admission for the particular disease of interest [7]. Research has shown that women with two or more comorbid medical conditions have significantly longer mean hospital stays than those with one or no comorbid medical condition [8]. It has also been documented that women over 60 years of age often have significant increase in comorbid medical conditions and significantly longer hospitalizations [8]. Unfortunately, there is paucity of data on admission lifetime for most clinical conditions especially gynaecological cancers which implies that local information is unavailable.

This study therefore aimed to assess the distribution of different types of genital cancers using the admission register from the Medical Records department and assess the survivorship of cancer patients and to identify their prognostic factors. Available data on patients with gynaecological cancers, who were admitted to the gynaecological wards of the University College Hospital, (UCH), Ibadan, were fitted into a Cox regression model by using the admission lifetime as the response variable and patient's status on discharge as the status censored parameter. Additionally, the relationships between cancer types, admission lifetime and patients' age were explored. The study has enabled us add to the existing body of knowledge on the duration and frequency of admission of cancer patients and the impact of such admissions on the overall outcome.

Methods and model specification

Study site and population

The site of this study was the University College Hospital, Ibadan – a leading tertiary healthcare centre for cancer care in Nigeria. There were 823 gynecological cancer patients admitted on the gynaecological and radiation oncology wards between January 1, 1995 and December 31, 2014 according to available medical records. Information on patients' age, cancer type, admission lifetime and patient's status as at the time of censoring (in days) were retrieved for retrospective analysis.

Censoring

In this study, patients were censored when they were reported dead or discharged from the hospital. Moreover, all patients that were alive as at the end of the data collection were right censored in accordance with the principle that patient would be right censored when the expected event was yet to take place even if the participant left the study before its completion [9]. This implied that all patients that were still on admission by December 31, 2014 were right censored.

Model

The Cox regression model was adopted using admission for gynaecological cancer data retrieved from the medical records for patients in the UCH, Ibadan. The data comprised of 823 cases and the cancer types were categorized into cervix, ovary, trophoplastic placental, uterus, vagina, and vulva. Survival probabilities were estimated in this study for the type of cancer and also for the different age categories of the patients.

Survival function S (t):

The survival function models the probability of an individual surviving beyond a specified time, t. The survival curve, S(t), is often plotted to graphically represent the probability of an individual's survival at varying time points.

The statistical expression of the survival function is given as:

$$S(t) = p(T > t) = 1 - F(t) \qquad (1)$$

Where t is specific time, T is a random variable denoting the time of death, F(t) is the probability distribution function and it is given by

$$F(t) = \Pr(T \le t) \qquad (2)$$

The Semi-parametric survival analysis

One of the most popular regression technologies for survival analysis is Cox proportional hazards regression also known as cox regression model [10], which is used to relate several risk factors or exposures, considered simultaneously, to survival time. In a Cox proportional hazards regression model, the measures of effect is the hazard rate, which is the risk of failure (the risk or probability of suffering the event of interest), given that the participant has survived up to a specific time.

The Cox proportional hazards model is a semi-parametric model as there is no assumption about the shape of the baseline hazard function. Therneau and Grambsch (2000) stated that the Cox Regression procedure is useful for modeling the time to a specified event, based upon the values of given covariates [10] while one or more covariates are used to predict a status (event). The assumptions for appropriate use of the Cox proportional hazards regression model included the independence of survival times between distinct individuals in the sample, presence of a multiplicative relationship between the predictors and the hazard as well as a constant hazard ratio over time.

The Cox proportional hazard regression model can be written as follows:

$$h(t;x) = h_0(t)exp(\beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_p X_p) \quad (3)$$

Where

$h(t;x)$ is the expected hazard at time t,

$h_0(t)$ is the baseline hazard and represented the hazard when all of the predictors (or independent variables) $x_1, x_2 \cdots x_p$ are equal to zero.

Research hypotheses and statistical analysis

This study aimed to evaluate the hypothesis of no difference in the survival experiences of individual's overall outcome with respect to the admission lifetime, age group and cancer type. In addition, it aimed to determine the effect of possible interaction between age group and cancer type. The statistics estimated for each of the cancer type and median lifetime, for alive and dead patients included the Kaplan-Meier estimates and boxplot showing median admission days for alive and dead patients. The study used some model criteria such as p-value, log rank test, Gehan–Wilcoxon test, r-square, likelihood ratio test, Wald test and score test to check for the efficiency of these results.

Results

This study explored the available information on a total of 823 patients in order to estimate their admission lifetime as well as its relationship to their survival. Overall, 611 (74.24%) were right censored which implied that they were alive while 212 (25.76%) were died (Table 1). Analysis of cancer type and age group are also presented in table 1 and it shows the sites of the cancer as cervix in 440 out of which 125 (28.41%)

Table 1: Descriptive Statistics by Patient's Status, Cancer Type, and Age Group

Item	Levels	Frequency (%)	Status at Censoring	
			Alive	Dead
Overall (n=823)			611(74.2%)	212 (25.8%)
Cancer Type	Cervix	440(53.5%)	315	125
(Frequency)	Ovary	224(27.2%)	177	47
	Placental	67(8.1%)	42	25
	Endometrium	77(9.4%)	65	12
	Vagina	4(0.5%)	4	0
	Vulva	11(1.3%)	8	3
	Total	823	611	212
Age group (Years)	<20	11(1.3%)	8	3
	20-29	31(3.8%)	26	5
	30-39	118(14.3%)	89	29
	40-49	210(25.5%)	166	44
	50-59	205(24.9%)	151	54
	>=60	248(30.1%)	171	77
	Total	823	611	212
Cancer Type	Median Admission Lifetime (Days)			
	Cervix	11.0		
	Ovary	9.0		
	Placental	15.5		
	Endometrium	14.0		
	Vagina	13.0		
	Vulva	36.0		

were dead, ovary had 224 patients with 47 (20.98% dead) and vulva had 11 patients with 3 (27.27%) dead. According to age group of the patients, patients with age group < 20 years were 11 with 3 (27.27% dead); 20-29 years were 31 with 5 (16.13% dead) and age group 60 years and above were 248 with 77 (31.05%) dead.

< 0.05 and 0.045, < 0.05 respectively. These showed that there was a statistically significant difference in the survival experiences of individuals between the interaction effects of age group and cancer type groups and the admission lifetimes.

In table 3, the Cox Proportional Hazard model estimations with "Cancer Type" and "Age" as covariates are presented. The model's statistics are presented as $R^2 = 0.018$, likelihood ratio test = 15.16 with p-value 0.0017, Wald test = 15.35 with p-value of 0.0015, and the Score test = 15.81 with p-value of 0.0012. These were all significant at 1% α-level of significance and it is therefore obvious that the explanatory variable, age, is highly significant at the 1% level of significance with p-value of 0.0001. Also significant at this level are the estimated model's statistics. Thus, factor age can be considered to affect survival probabilities of the patients.

Table 2: Survival experiences of individuals by cancer types, age group and interaction

Model	Value	df	p-value at 5%	Remark	Decision (H_0)
(Cancer type)					
log-rank test	13.2	6	0.0404	sig.	Reject
Gehan-Wilcoxon	12.9	6	0.0449	sig.	Reject
(Age group)					
log-rank test	15.8	3	0.0012	sig.	Reject
Gehan-Wilcoxon	14.2	3	0.0026	sig.	Reject
(Interaction)					
log-rank test	37.1	23	0.0320	sig.	Reject
Gehan-Wilcoxon	35.6	23	0.0452	sig.	Reject

The comparison of "Cancer Type" and "Age Category" using log-rank test and Gehan-Wilcoxon test are as shown in table 2. This result was used to check the hypotheses of whether there is difference in the survival experiences of patients between the cancer site and age groups at the admission lifetimes as well as their interaction. The value for log-rank test and and Gehan-Wilcoxon test were 13.2 and 12.9 with p-values of 0.040, < 0.05 and 0.044, < 0.05 respectively. These showed that there is a statistically significant difference in the survival experiences of individuals between the cancer type groups during the admission time. The value for log-rank test and and Gehan-Wilcoxon test were 15.8 and 14.2 with p-value of 0.0012, < 0.05 and 0.002, < 0.05 respectively thus demonstrating a statistically significant difference in the survival experiences of individuals between the age group during the admission time. The value for log-rank test and and Gehan-Wilcoxon test are 37.1 and 35.6 with p-value of 0.032,

In addition, results obtained showed that only ovarian cancer from the cancer type was significant at the 5% significance level (p=0.0019). This indicates that ovarian cancer is significant when considering the admission lifetime of the patients because people with this cancer type are more likely to stay in the hospital because of surgery and chemotherapy more than other cancer types. However, it is worthy to further examine

Table 3: Cox Proportional Hazard Model

Covariates		β	$HR = e(\beta)$	P-value	Interval (Lower - Upper)
Age		0.0201	1.0203	0.0002	1.0100 – 1.0310
Cancer type: Ovary		-0.5348	-0.0586	0.0079	0.4181 – 0.8210
Interaction	Age	0.0186	1.0188	0.0005	1.0082 – 1.0300
	Ovary	-0.4284	0.6516	0.0103	0.4697 – 0.9040

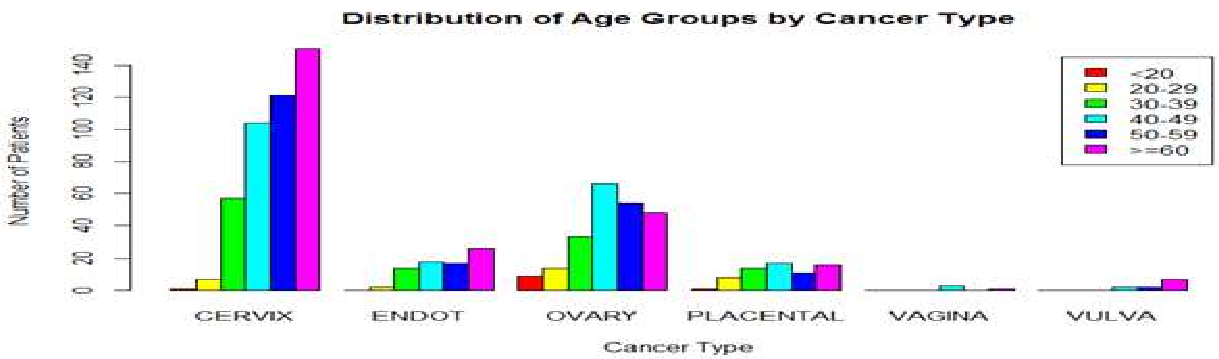

Fig. 1. Histogram plot for patient's age group by cancer type

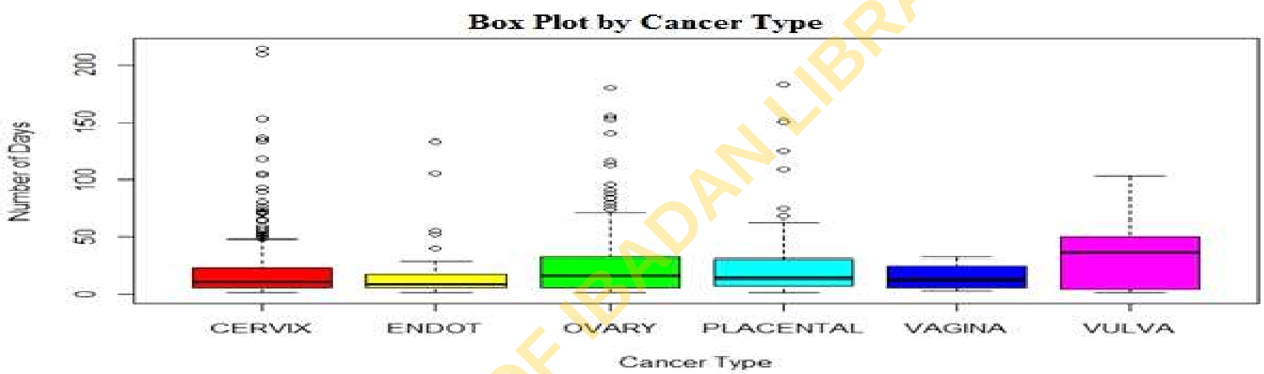

Fig. 2. Box plot for patients by cancer type

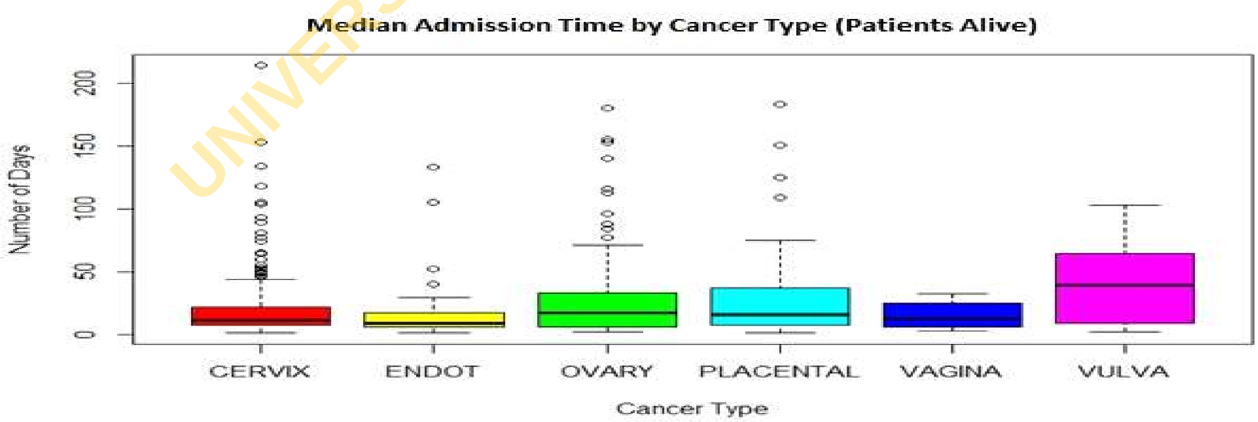

Fig. 3. Boxplot for patient's median admission time by cancer type (patients alive)

the factor variable cancer type in a model that contains age and cancer type as covariates. The output of the relevant model also showed endometrium (p-value = 0.1956), cervix (p-value = 0.4334), trophoblastic (p-value = 0.4334), vagina (p-value = 0.9905) and vulva (p-value = 0.2987) with non significant value. Ovary and age were also noted to remain statistically significant at the 1% alpha significant level.

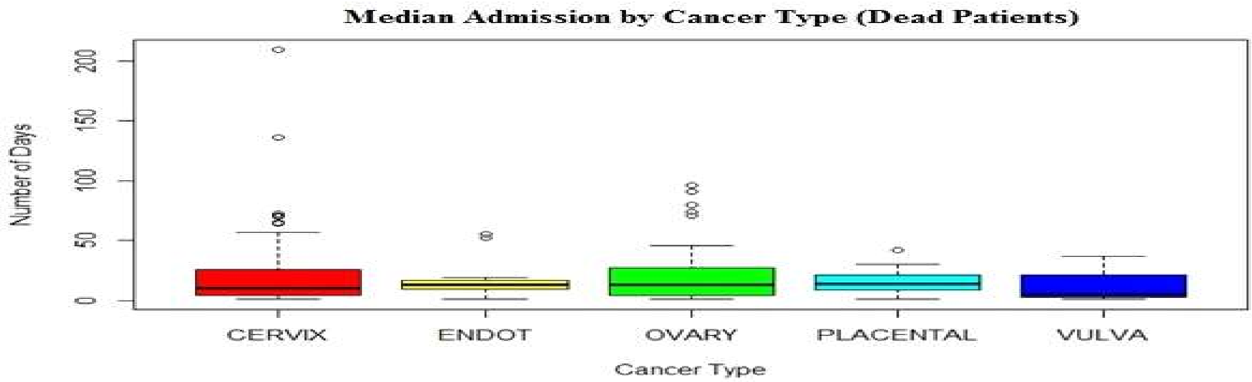

Fig. 4. Boxplot for patient's median admission time by cancer type (dead patients)

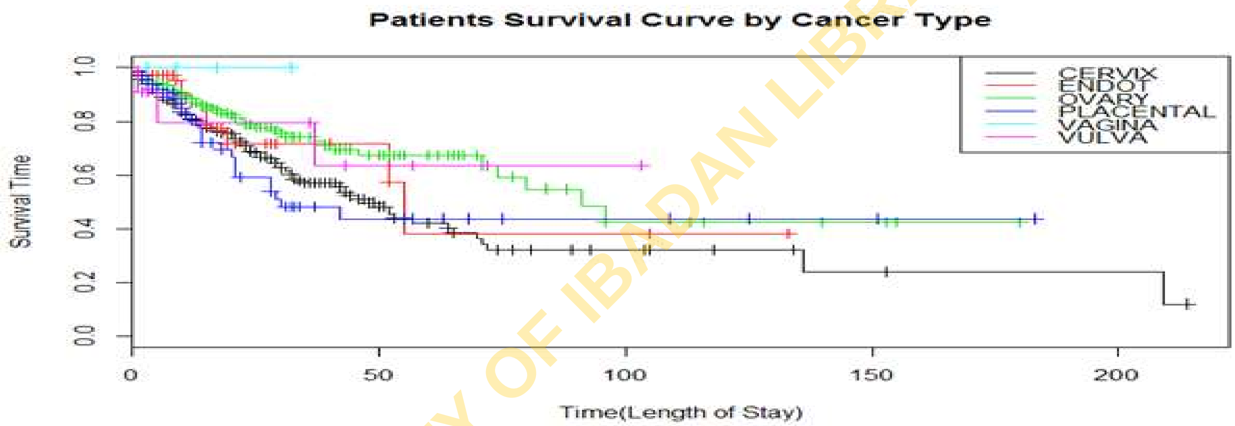

Fig. 5. Kaplan Meir's curve for patient's admission lifetime by Cancer Type

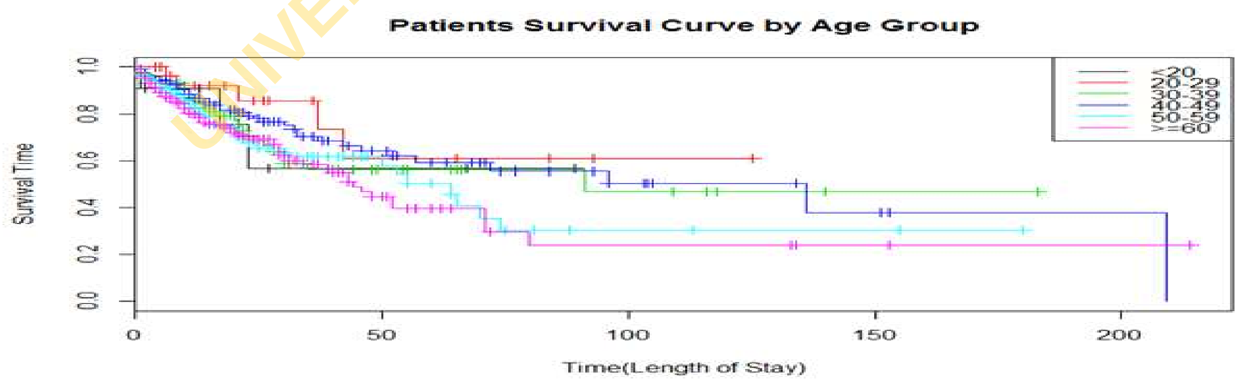

Fig 6: Kaplan Meir's curve for patient's admission lifetime by Age group

Figure 1 shows the distribution of age group by their cancer type while figure 2 shows the admission lifetime by cancer type. Figures 3 and 4 demonstrate the median admission lifetime by cancer type for alive and dead patients respectively while figures 5 and 6 show the Kaplan Meier's curve for patient's admission lifetime by cancer type and age group respectively.

Finally, as covariates were included in the Cox model and re- fitted, the results obtained indicated that the appropriate model for predicting cancer patients' survival probabilities is the last model which gives the estimated parameters at the 5% level of significance as significant.

Discussion

Our findings are significant among the patients in terms of age and cancer type contributing to the length of stay of each patient and the overall outcome which is in agreement with Chakalova (2015) who asserted that age of patients and different chronic diseases are relevant to the treatment strategies used [11]. This underscorsd the essence of ensuring special considerations in the management plan of elderly cancer patients which should be decided before commencing treatment. In other words, factors that will determine the length of stay at the hospital and their survival experiences depend on age group and cancer site.

Using age group as the covariates, the age group 60 years and above significantly affected the length of stay of the patients at the hospital which eventually has effects on their survival experiences. This finding is in agreement with the report of Tarney *et al* (2012) in a study on impact of age at diagnosis in endometrial cancer patients [12]. Although, their results indicated that aggressive histology and molecular features were more common in older age group and intervention at early ages may be necessary, our data were limited in the non-availability of histology reports of the cancer subtypes which would have enabled more comparison.

From the study by Dean *et al* (2001), it was equally reported that women aged 60 years and above were likely to have longer admission lifetime for female genital cancer surgeries than their younger age counterparts [8] and this is similar with our findings that age group from 60 years above significantly affected the length of stay at hospital with subsequent impact of this admission lifetime on their survival experiences in the gynaecology ward.

On the other hand, using the cancer type as the covariates, ovarian cancer was found to significantly affect the patients' length of stay which is similar to the observation reported by the Surveillance, Epidemiology and End Results (SEER, 2014) program of the National Cancer Institute which was based on available data through 2014. Recent statistics projections from the American Cancer Society estimated that in 2018, about 22,240 new cases of ovarian cancer will be diagnosed and 14,070 women will die of ovarian cancer in the United States [13]. Also, SEER reported that ovarian cancer is the fifth leading cause of cancer-related death among women, and is the deadliest of gynecologic cancers with life-time risk of occurrence for a woman being 1 in 79 while the life time risk for dying is 1 in 109.

Gardiner (2010) asserted that, although the Cox model is non-parametric to the extent that no assumptions were made about the form of the baseline hazard, there are still a number of important issues which need be assessed before the model results can be safely applied [14]. First and foremost is the issue of non-informative censoring and to satisfy this assumption, the design of the underlying study must ensure that the mechanisms giving rise to censoring of individual subjects are not related to the probability of an event occurring [14,15]. This indirectly implies that care must be taken to ensure that continuation of follow-up is independent of participants' medical condition.

We can therefore conclude from the Cox regression models fitted so far that the only factors that affect cancer patients' survival based on the available data used for the study are: age, cancer type (ovary) and age group 60yrs and above. Therefore, the appropriate model for predicting cancer patients' survival probabilities is the last model. It was also discovered that ovarian cancer is the deadliest of gynaecological cancers and this means that survival experiences of woman's lifetime at hospital after medical intervention will be determined by the type of cancer. Since the survival rate for ovarian cancers is much lower than other cancers that affect women, priority should be given to patients with this cancer. In addition, the strength of our study is its ability to provide baseline data for future review of patients' overall outcome with respect to cancer management.

However, this study was limited to data retrieved from Medical Record department of patients admitted to gynaecology ward of UCH and unfortunately, some were either missing or incomplete. The data were basically for patients admitted for care and the available covariates were limited to age and cancer type. Other variables like patients' education, treatment history and some other relevant variables could have been useful for measuring their impact on the admission lifetime of these patients. Some specific histological details were unknown as some germ cell tumors for example were mixed up with epithelial ovarian cancers. In addition, it was not all cases of cervical cancer that were admitted as some were referred to the radiation oncologists for radiotherapy which is often provided on outpatient basis. We suggest further longitudinal studies with these and other details documented.

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Received = 06th December 2018
Accepted = 24th July 2020