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SURVIVAL TIMES OF BREAST CANCER PATIENTS IN NIGERIA: APPLICATION OF COX AND PARAMETRIC SURVIVAL MODELS

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ABSTRACT: *In this study, we modeled the survival time of breast cancer patients in Nigeria using five survival models, namely the Cox model, the exponential model, the lognormal model, the logistic model, and the Weibull model. The Akaike information criterion (AIC) and Bayesian information criterion (BIC) were used as performance metrics for the selection of the best-fit model. The Cox proportional hazard (CPH) model was the best model for the cancer data. We also noted that the median patient survival time was 295 days. The Kaplan-Meier test was used to compare the survival curves. The CPH model was used to model the data. We observed that the neoadjuvant therapy covariate had a significant effect on the survival time of the breast cancer patients ($p < 0.05$). This suggests that it has a considerable impact on Nigerian breast cancer patients' survival rates. This study could result in more efficient cancer treatments and has substantial implications for the management and care of breast cancer patients in Nigeria. It further extends the work of Awodutire et al. (2017).*

KEYWORDS: Breast cancer, Survival times, Modeling, Censoring, Nigeria.

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INTRODUCTION

Breast cancer is the most common cancer among Nigerian women. In 2020, the World Health Organization (WHO) noted that an estimated 33,000 new cases of breast cancer and 17,000 deaths occurred in Nigeria, thereby making breast cancer account to about 25% of all cancer cases in Nigeria. New cases of breast cancer worldwide were estimated to be 2.3 million, with 685,000 deaths according to the International Agency for Research on Cancer (IARC) in 2020. Breast cancer accounts for about 11.7% of all new cases and 6.7% of all cancer deaths worldwide. Gagnon et al. (2016) indicated that breast cancer is the leading cause of cancer-related deaths in women worldwide, affecting approximately 1.7 million women annually. Eletxigerra et al. (2016) noted that amongst the women, it is the second leading cause of death. With more instances being reported each year, breast cancer is becoming a bigger worry in Nigeria (JokoFru et al., 2020). A statistical technique called survival analysis is utilized to track the interval before the event of interest (breast cancer-related death) occurs. In recent years, it has become more common to investigate the rates of survival of the breast cancer patients in Nigeria utilizing the method of survival analysis models like Cox and Parametric survival models. These models make it possible to calculate the likelihood of surviving and identify variables that might affect survival rates. By using these models on breast cancer data from Nigeria, it is possible to get important knowledge about the progression of the illness, the effect of treatment on survival, and potential patient prognostic markers. It is crucial to take into account the numerous contributing reasons to Nigeria's high incidence rate as well as the efforts being done to tackle the problem in order to better comprehend the situation here (Makanjuola et al., 2014; Joko-Fru et al., 2020). Lack of awareness of the illness is one important factor that could contribute to the high incidence of breast cancer in Nigeria (Zaidi & Dib, 2019). Our study intends to use the Cox and parametric survival models to: (i) fitting five survival models on Nigeria cancer data; (ii) selecting the model that best fits the cancer data using Akaike Information Criterion (AIC) and Bayesian Information Criteria (BIC) criteria; and (iii) modeling the cancer data with the selected model to obtain cancer prognosis estimates.

RELATED WORKS

Amongst the parametric survival models, Lognormal has been selected as the best fitting model for cancer data (Vallinayagam et al., 2014; Mohseny et al., 2017). Awodutire et al. (2017) used parametric survival models to investigate the survival times of the Nigerian cancer data. They observed that the stages at which the cancer patients reported to hospital were significant at 0.05. According to a study by Okoye et al. (2017), many women in Nigeria are not familiar with the symptoms of breast cancer, and as a result, they may delay seeking treatment until the disease has reached an advanced stage. A lack of access to quality healthcare is another factor that may contribute to Nigeria's high incidence of breast cancer. Many women in Nigeria live in rural areas where there are limited healthcare facilities, and quality care is not given even when health care is accessed (Adebamowo et al., 2010; Azubuike et al., 2018; Ferlay et al., 2010). This can result in women receiving a late diagnosis, which can negatively impact their chances of survival (Olasehinde et al., 2019; Adisa et al., 2012; Jedy-Agba et al., 2016). Despite these challenges, there have been several efforts to mitigate breast cancer in Nigeria. For example, the Nigerian government has established the National Breast Cancer Control Program, which aims to improve awareness

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about the disease as well as women's access to quality healthcare (Adebamowo et al., 2010). Additionally, various non-governmental organizations and advocacy groups have been working to raise awareness about breast cancer in Nigeria and encourage women to seek early detection and treatment (Panda & Jalali, 2018).

A statistical technique called survival analysis is used to determine when a particular event, like death or the recurrence of a disease, will occur (Fischer et al., 2017). It is frequently used in medical studies to look at how long an illness, such breast cancer, takes to manifest (Fischer et al., 2017). To assess breast cancer data, a variety of survival models can be utilized, including the following: (i) Cox Proportional Hazard (CPH) Model: It is one of the most popular survival models (Cox, 1972). It is a regression model that assumes the hazard function, which represents the relationship between a set of predictor variables and the likelihood that the relevant event will occur at a particular time. Age, tumor stage, and treatment methods are possible predictor variables in the context of breast cancer. Using the Cox model's estimation of each predictor's impact on the hazard function, the hazard functions of groups with different predictor values can be compared.

(ii) The Fine and Gray Model: The Fine and Gray model is a Cox model extension that takes into consideration the presence of competing risks (Fine & Gray, 1999). When a patient can suffer more than one sort of event, such as death or recurrence, then competing risks are said to have occurred. The Fine and Gray model estimates the hazard function for each type of occurrence, making it a helpful tool for assessing breast cancer data in which patients may die or recur.

(iii) The Accelerated Time Failure (AFT) model: This proposes that the time to an event is a transformation of a random variable with a known distribution. The AFT model can be used in the context of breast cancer to estimate the effect of predictor variables on the transformation of time into an event. This provides for a more direct comparison of predictor factors' effects on event time than the hazard function. The Exponential model, Log Normal model, and Log Logistic model are AFT models. The Weibull model is both Proportional Hazard (PH) and AFT.

Cox regression and parametric survival models are commonly used in medical research to estimate the probability of survival for patients with a specific disease (Eze et al., 2017; Adekeye et al., 2015). In Nigeria, several studies have applied these models to investigate the prognosis of cancer patients and identify risk factors for poor survival outcomes (Eze et al., 2017; Adekeye et al., 2015). These studies demonstrate the usefulness of Cox regression and parametric survival models for analyzing cancer survival in Nigeria and provide important insights into the factors that influence survival outcomes for breast cancer patients in this population (Eze et al., 2017; Adekeye et al., 2015). To that end, the following objectives were set: (i) fitting five survival models on Nigeria cancer data using AIC and BIC criteria; (ii) selecting the model that best fits the cancer data; and (iii) modeling the cancer data with the selected model to obtain cancer prognosis estimates.

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MATERIAL AND METHODS

Data Collection

Data for the study were collected at the Ladoke Akintola University of Technology Teaching Hospital in Osogbo, Osun State, Nigeria. The data set includes 89 chosen patients with breast cancer incidences recorded at the hospital between 2009 and 2014. It is appropriately suppressed after one (1) year of diagnosis. The survival time is calculated from the patient's day of admission to the day of discharge/last contact (alive, loss of follow-up, or death).

The data variables are listed below:

1. **TIME (IN DAYS)**: This determines how long the patient will live. The survival time is calculated as the difference between the date of admission to the hospital for treatment and the date of last contact. Days are used to measure time.
2. **AGE OF PATIENTS**: It keeps a record of the patients' ages (in years) at the time of their hospitalization.
3. **CENSOR**: When survival time is uncensored, it is recorded as 1 and when it is censored, it is recorded as 0.
4. **AGE AT MENARCHE**: This is the age when the patient first had menstrual flow. It is measured in years.
5. **BREASTFEEDING**: This section contains the patient's average number of years spent nursing.
6. **DETECTION**: This variable stores information on the tumor's development phases at the time of presentation. There are four stages: I, II, III, and IV. It was divided into two stages: Stage I and II (Early Detection), and Stage III and IV (Late Detection).In this work, we designated Early Detection -1 and Late Detection -2 for ease of computation.
7. **CONTRACEPTIVE**: Has the patient ever taken a contraceptive? 1 - Yeah, 2 - No.
8. **NEOADJUVANT**: The current state of Neoadjuvant administration. 1 - Yeah, 2 - No.

Methods

Cox Proportional Hazard Model

The hazard function illustrates the Cox model. It is represented by:

$$h(\mathrm{t}) = h_0(t) \times \exp\left(b_1 x_1 + b_2 x_2 + \cdots + b_p x_p\right)$$

Where, $h(t)$ the hazard function determined by a set of p covariates $\left(x_1, x_2, \cdots, x_p\right)$, t is the survival time, h_0 is the baseline hazard, $\left(b_1, b_2, \cdots, b_p\right)$ determine the effect of covariates

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Exponential Distribution

The density, survival, and hazard functions of a random variable T with a lognormal distribution are given as:

$$f\left(t,\lambda\right)=\lambda\exp\left(-\lambda t\right)$$

$$S\left(t,\lambda\right)=\exp\left(-\lambda t\right)$$

$$h\left(t,\lambda\right)=\lambda$$

Where λ>0.

Lognormal Distribution

The density, survival, and hazard functions of a random variable T with a lognormal distribution are given as:

$$\mathrm{f}\left(t,\mu,\sigma^2\right)=\frac{\exp\left[-\left(\log t-\mu\right)^2/2\sigma^2\right]}{\sqrt{2\pi\sigma t}}$$

$$S\left(t,\mu,\sigma^2\right)=1-\phi\left(\frac{\log t-\mu}{\sigma}\right)$$

$$h\left(t,\lambda,\gamma\right)=\frac{f\left(t\right)}{S\left(t\right)}$$

Where $\sigma^2>0$

The application lognormal distribution in medicine research has gained wave. Lognormal distribution was applied in a study on the chronic lymphocytic and my

Log Logistic Distribution

The density, survival, and hazard function of a random variable T with a Loglogistics distribution are given as:

$$f\left(t,\lambda,\gamma\right)=\frac{\lambda\gamma t^{\gamma-1}}{\left(1+\lambda t^{\gamma}\right)^2}$$

$$S\left(t,\lambda,\gamma\right)=\frac{1}{\left(1+\lambda t^{\gamma}\right)}$$

$$h\left(t,\lambda,\gamma\right)=\frac{\lambda\gamma t^{\gamma-1}}{1+\lambda t^{\gamma}}$$

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Where $\lambda > 0, \lambda > 0$

The Loglogistic distribution has been proven to be suitable for analyzing time-to-event data according to the study of Gupta et al. (1999). A study also considered the maximum likelihood estimation as the most suitable parameter estimation method for the Loglogistic on a half-censored data (Zhou et al., 2007).

Weibull Model

The density, survival, and hazard function of a random variable T with a Weibull distribution are given as:

$$f\left(t,\lambda,\gamma\right)=\lambda\gamma t^{\gamma-1}\exp\left(-\lambda t^{\gamma}\right)$$

$$S\left(t,\lambda,\gamma\right)=\exp\left(-\lambda t^{\gamma}\right)$$

$$h\left(t,\lambda,\gamma\right)=\lambda\gamma t^{\gamma-1}$$

$$\lambda > 0, \lambda > 0$$

Weibull is a generalization of the exponential distribution. Due to the Weibull distribution decreases mortality ratio in patient group and is monotonic increasing, it is suitable for application in medicine and analysis of time-to-event data. In industrial engineering, the Weibull distribution is preferred for survival data analysis (Weibull, 1951).

Kaplan-Meiers Test

The Kaplan-Meier (KM) technique is a non-parametric method for estimating the likelihood of survival based on observed survival times (Kaplan and Meier, 1958).

The survival probability $S\left(t_i\right)$ at time t_i is computed as follows:

$$S\left(t_i\right)=S\left(t_{i-1}\right)\left(1-\frac{d_i}{n_i}\right)$$

Where, $S\left(t_i\right)$ = probability of being alive at t_{i-1}, n_i = number of patients alive just before t_i,

d_i = number of events at t_i, and $t_0=0, S\left(0\right)=1$.

The KM curve is a plot with the probability of survival against time. It has useful summary about the survival estimate such as median survival time.

Model Selection

The Akaike Information Criterion (AIC) and Bayesian Information Criteria (BIC) were used as performance metrics for the best model selection

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Akaike Information Criterion

The AIC is defined as:

$$AIC = -2\log(likelihood) + 2k$$

Where k is the number of model parameters. The model with the lowest AIC value is regarded to be the best suited model (Collett, 2003).

Bayesian Information Criterion

The Baysian Information Criteria is computed as follows:

$$BIC = -2\log(likelihood) + 2k * \log(n)$$

Where k is the number of parameters in the model and log (n) is the number of observations. The distribution which has the lowest BIC value is considered as best fitted model.

DATA ANALYSIS AND RESULTS

We used RStudio 2022.07.2+576 for the analysis of our study's data.

Table 1: Summary of the survival models with respective AIC and BIC.

S/N	Models	AIC	BIC
1	Cox Proportional Hazard (CPH)	414.56	426.15
2	Exponential	762.64	780.06
3	Log-normal	691.82	711.73
4	Log-logistic	693.38	713.29
5	Weibull	699.86	719.77

In Table 1, the AIC and BIC scores for each of the five models are displayed. The Cox model had the lowest AIC and BIC values, which were 414.56 and 426.15, respectively. The Cox model is regarded as the best survival model for our time-to-event data since it has the lowest AIC and BIC values. The Log-normal was the next survival model following the CPH model that had AIC and BIC values of 691.82 and 711.73 respectively. Log-logistic was next in line with AIC and BIC of 693.38 and 713.29 respectively. The Weibull was the fourth according to the performance with AIC and BIC of 699.86 and 719.77 respectively. Finally, the exponential model recorded the highest AIC and BIC of 762.64 and 780.06 respectively, making it the least performing survival model in this study.

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Table 2: Cox Proportional Hazard model estimates

Variables	Coefficient	Z	p-value
Age	-0.018	-1.229	0.219
Age at Menarche	0.057	0.925	0.355
Breastfeed	-0.473	-1.596	0.111
Contraceptive	-0.517	-1.742	0.081
Neoadjuvant	-0.603	-1.992	**0.046**
Detection	-0.619	-1.933	0.053

In Table 2, considering the p-value column of the Cox model summary, we observed that it was only the Neoadjuvant recorded ($p<0.05$). This implies that it has significant effect on the survival of breast cancer patients.

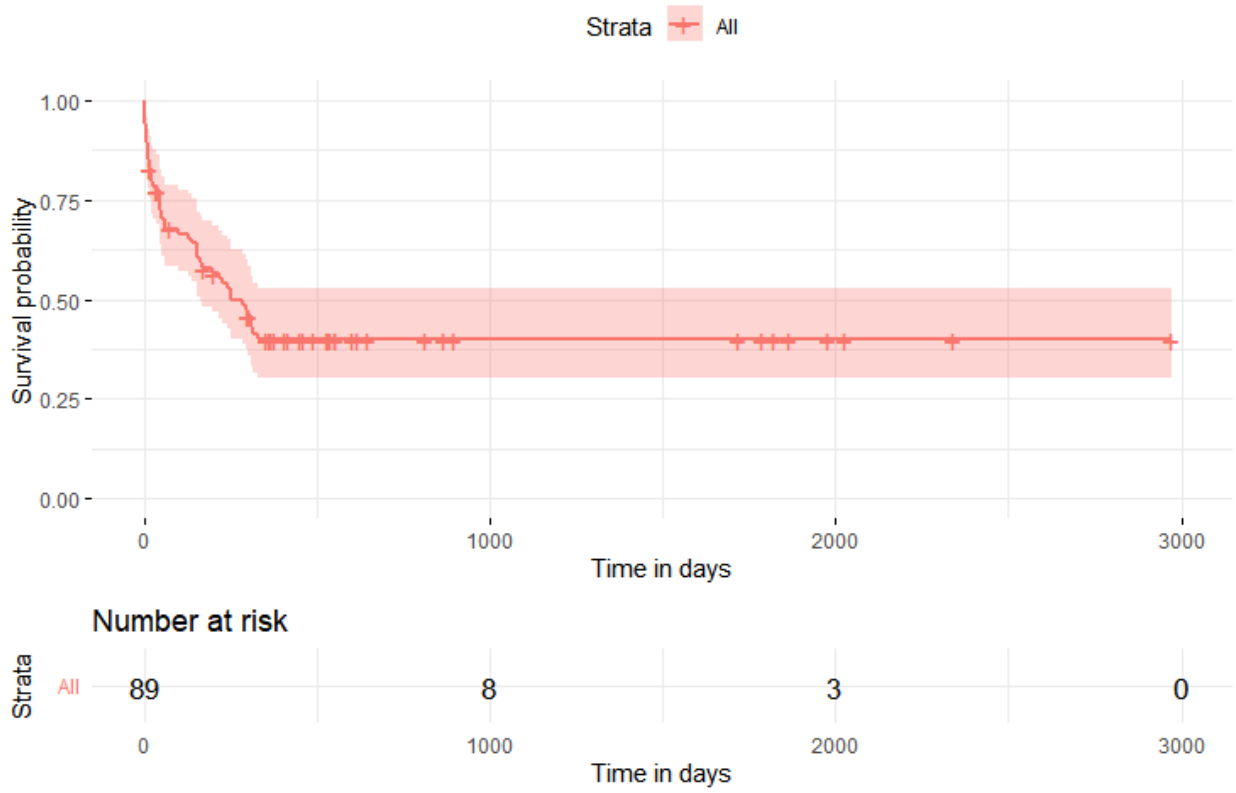

Figure 1: Survival Curve of the Cox Model

Figure 1 represents the survival curve of the best model. At risk at time zero (0), the number of patients at risk of death was 89. The number of patients keeps decreasing due to occurrence of event and censoring. From Figure 1, we observed that the median survival time was approximately 295 days.

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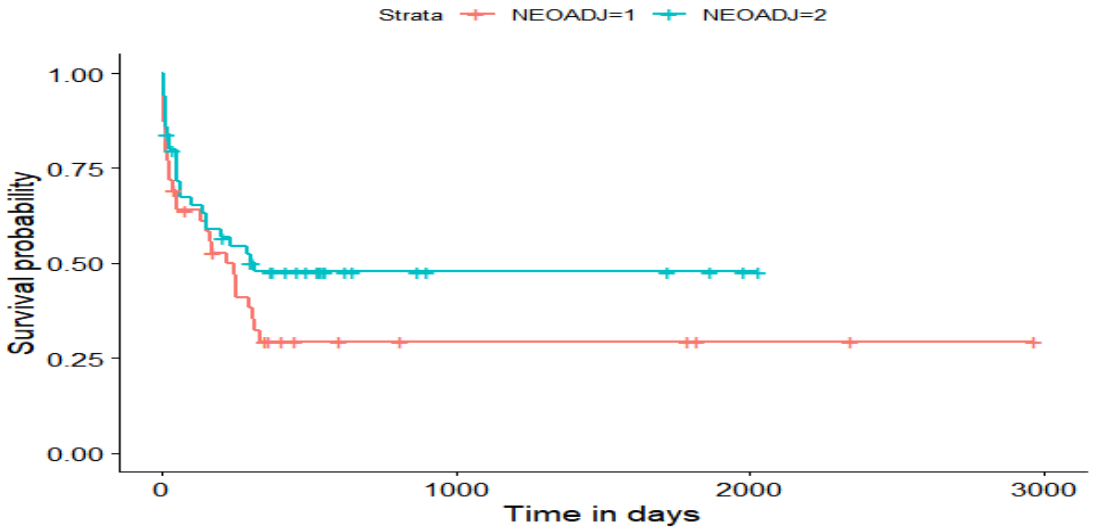

Figure 2: Survival Curve of the Application of Neoadjuvant

The Figure 2, depicts the survival curve of the covariate that have significant effect on the survival of the breast cancer patients under study. The **NEOADJ=1** indicates that it was applied, and **NEOADJ=2** indicates that the neoadjuvant was not applied to the patients.

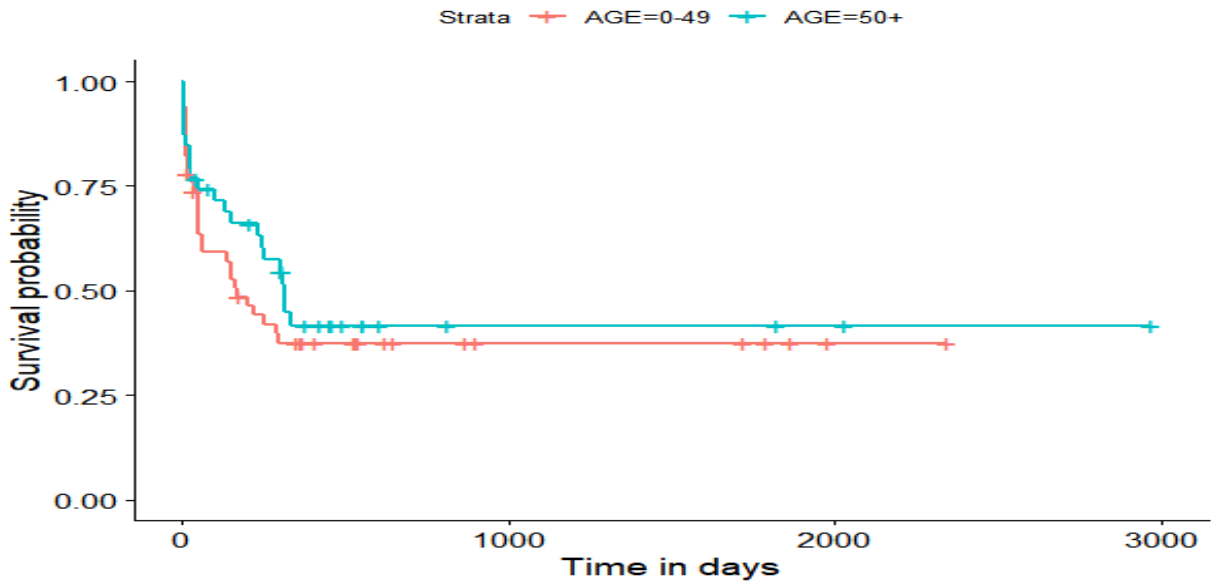

Figure 3: Survival Curve of the Age group

We divided the age into two groups, **AGE=0-49**, and **AGE=50+**. Looking at the survival curve, it was noticed that the age group **50+** have median survival time greater than the age group of **0-49**.

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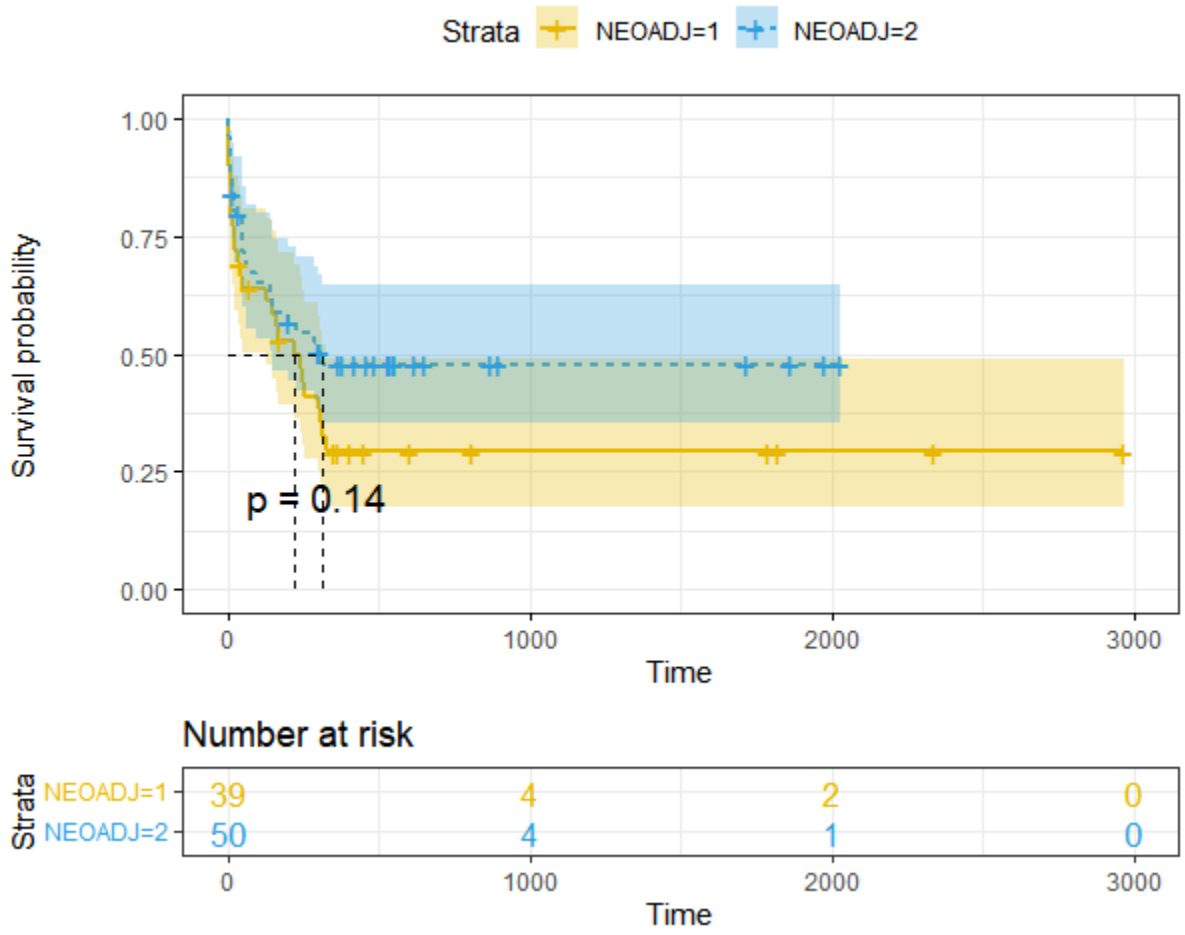

Figure 4: Kaplan-Meier Curve of the Application of Neoadjuvant

The vertical axis (y-axis) in Figure 6 depicts the survival probability, while the horizontal axis (x-axis) represents the time in days. The two lines represent the survival curves of patients who received neoadjuvant therapy (**NEOADJ=1**) and those who did not (**NEOADJ=2**). The vertical tick indicates that at that time, a patient was censored. A vertical drop in the survival curve indicates the occurrence of an event. The survival probability at time zero (0) is 1.0 (100% of the patients are alive). The median survival duration for patients who had neoadjuvant therapy and those who did not was 219 and 312 days respectively. This means that individuals who did not receive the neoadjuvant fared better than those who did. According to Figure 6, the log-rank test p-value is 0.14 (**p>0.05**). This shows that there is no statistically significant difference between patients who received the neoadjuvant and those who did not. This goes further to explain that the difference in the median survival times of 219 and 312 days are not statistically significant.

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DISCUSSION

From Table 1, we selected the Cox Proportional Hazard (CPH) model as the best fitting model for the Nigerian breast cancer data as opposed to Vallinagam et al. (2014) and Mohseny et al. (2017) that selected Lognormal as the best fitting model for different cancer data. We explored further using the Cox model, and from the model summary, we observed that neoadjuvant had a significant effect on the survival the breast cancer in Nigeria ($p<0.05$). This further extends the work of Awodutire et al., (2017). The Survival curve of the Cox model was presented in Figure 1. In the figure, we observed the decrease in the number of patients from 89 to 0 due to occurrence of the event of interest and censoring. We also observed that the median survival time for the breast cancer patients are approximately 295 days. Furthermore, we plotted the survival curve of the application of the neoadjuvant in Figure 2. From Figure 2, it can be observed that the median survival time of those that did not take the neoadjuvant (NEOADJ=2) was greater than those that took the neoadjuvant (NEOADJ=1). We divided the age into two groups: AGE=0-49, and AGE=50+. From Figure 3, we observed that the age group 50+ has median survival time slightly greater than the age group of 0-49 age group. Finally, we plotted the Kaplan-Meier curve of the application of the neoadjuvant. We observed that 50 patients took the neoadjuvant and 39 patients did not take the neoadjuvant. From the curve, the log-rank test recorded ($p>0.05$) which indicates that there is no statistically significant difference between the patients who received the neoadjuvant and those who did not receive it.

CONCLUSION

Finally, this study revealed the effectiveness of CPH and parametric survival models in assessing the survival times of breast cancer patients in Nigeria. The CPH model was shown to be the best-fitting model to the Nigerian breast cancer data. The Kaplan-Meier curve was employed to compare the survival curve of the application of neoadjuvant, which tested significant (**$p<0.05$**) in the best model. We also discovered that the patients' median survival duration was 295 days. The study discovered that neoadjuvant treatment has a significant impact on patient survival time according to the CPH model estimates. The study's findings have important significance for the management and treatment of breast cancer patients in Nigeria, since they provide insights into factors that can influence patient outcomes. Further research is needed to determine the efficacy of various treatment techniques and interventions in improving survival rates for breast cancer patients in Nigeria. Overall, this study adds to our understanding on the best fitting model for the Nigeria Breast Cancer patients. It found out that the application of the neoadjuvant has a significant impact on the survival time of breast cancer patients. Therefore, the study has the potential to enhance breast cancer patients' outcomes in Nigeria and beyond.

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RECOMMENDATIONS

The study recommends that the Nigerian healthcare should improve the data recording process. Currently, there is not enough breast cancer data to adequately explore the area of research locally. Further research is needed to determine the efficacy of various treatment techniques and interventions in improving survival rates for breast cancer patients in Nigeria. Efforts should also be made to increase access to healthcare services and resources for breast cancer patients in Nigeria, ensuring that all patients have access to adequate care and treatment. Overall, this study adds to our understanding of breast cancer management in Nigeria, and its findings have substantial implications for improving patient outcomes and lowering the disease's burden in the country.

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Data Availability: The data for this study is available [1].

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