International Journal of Community Medicine and Public Health
Sule GI et al. Int J Community Med Public Health. 2023 Oct;10(10):3459-3464
http://www.ijcmph.com
pISSN 2394-6032 | eISSN 2394-6040

DOI: https://dx.doi.org/10.18203/2394-6040.ijcmph20233069

Original Research Article

Accelerated failure time survival model for prostate cancer

George I. Sule[1]*, Angela U. Chukwu[1], Felix C. Akanno[2]

[1]Department of Statistics, University of Ibadan, Ibadan, Nigeria
[2]Department of Statistics, Federal University of Technology, Owerri, Nigeria

Received: 16 June 2023
Accepted: 11 September 2023

***Correspondence:**
George I. Sule,
E-mail: georgeisule@gmail.com

ABSTRACT

Background: Prostate cancer is the second most common cancer in men globally and ranks sixth among male cancer-related deaths. This study utilized survival analysis to assess post-diagnosis outcomes, aiming to enhance prostate cancer patient longevity. Insights were gained by determining median survival times, identifying prognostic factors, and applying an AFT model to prostate cancer data.
Methods: The study collected data from 502 prostate cancer patients featured in a 1980 paper by D. P. Byar and S. B. Green, focusing on stage 3 or 4 cases. Over six years, they monitored these patients' survival under varying estrogen doses, analyzing 15 variables. Data import was done using excel, R and SPSS were used for the analysis. Utilizing the Kaplan-Meier method and AFT models, the study identified predictive factors and determined the most suitable model for prostate cancer analysis.
Results: Among the 502 patients, 70.7% died, and 29.3% were right-censored, with a median survival of 35 months. Factors enhancing survival included a 1.0 mg estrogen dose, higher body weight, and elevated serum hemoglobin levels. In contrast, age, tumor size, cardiovascular disease history, and a composite index of stage and histology grade were associated with reduced survival odds in prostate cancer patients.
Conclusions: Prostate cancer patients had a median survival of 35 months, with survival rates at 60 months (31.7%) and 75 months (23.2%). The 1.0 mg estrogen dose proved most effective among tested doses. The Weibull AFT model, with an AIC score of 3469.032, was the best-fit model.

Keywords: Prostate cancer, Survival analysis, Accelerated failure time

INTRODUCTION

Prostate cancer was the second most frequent cancer in men worldwide and the fifth greatest cause of cancer-related death in 2018, with an estimated 1.3 million new cases and 359,000 related deaths.[1] The risk of dying from prostate cancer in Western Africa is the fifth highest in the world. Nigeria has the largest economy and population in the area. Prostate cancer is the most prevalent and lethal cancer in Nigerian males, with 32·8 incidence and 16.3 fatalities per 100,000 men. With an estimated 80% of Nigerians incurable upon diagnosis, this is more than twice as deadly as it is in North America.[2] And it is estimated that 16.48% of men will be diagnosed with prostate cancer at some point during their lives.[3] Shah et al conducted a study at the Universiti Kebangsaan Malaysia medical center in Kuala Lumpur to assess prostate cancer patients' survival rates and identify the predictive markers. Regardless of stage or treatment, individuals with prostate cancer had 5- and 10-year overall survival rates of 77.8 and 65.5%, respectively. Predictors of survival age were ≥75 years Gleason score ≥8 and complications of cancer metastasis.[4]

Survival analysis techniques have been used to measure the risk, hazards, and average survival time for cancer patients. The common research involving cancer is based on time called the survival time. The term ‘survival time’

is used in reference to the number of days, weeks, months and years from the time patient's observance begins until death takes place. Usually in survival studies, the patients are kept over a long period of time, so other factors are important to be still continual over the period. Dependent variable within the survival analysis is composed of two attributes namely, time-to-event as well as event status. An endpoint occurs either when the event occurs or when the follow-up time has ended.

Survival studies evaluate group of patients' overall performance in terms of their quality and length of life after diagnosis/therapy. It provides summary of demographic differences in terms of age, ethnicity, socioeconomic position, stage of diagnosis, therapy etc. To monitor and assess cancer control program, it is crucial to have knowledge of survival in addition to incidence and clinical stage at presentation. Lower survival rates in developing nations result of poor patient compliance, budgetary restrictions, limited treatment facilities, inadequate screening facilities, advanced illness stages at presentation and lack of knowledge.[5]

This study was conducted to determine median survival times, and the prognostic factors for prostate cancer, and to fit an accelerated failure time (AFT) model to prostate cancer data. In order to focus efforts on achieving universal prostate cancer screening and treatment, policymakers will benefit from findings of current study.

METHODS

Data for patients receiving hormone therapy were gathered from the report of the 1980 publication "The choice of treatment for cancer patients based on covariate information: Application to prostate cancer" by D. P. Byar and S. B. Green.

In this prostate cancer study, inclusion criteria encompass patients who have received a histological diagnosis of prostate cancer, ensuring diagnostic accuracy. The focus is on individuals with stage 3 (locally advanced) or stage 4 (metastatic) prostate cancer, acknowledging their potential for advanced disease management. Patient inclusion is restricted to those observed and diagnosed within a predefined time frame, promoting data consistency. Conversely, exclusion criteria pertain to patients with concurrent cancer diagnoses other than prostate cancer, early-stage prostate cancer (e.g., stage 1 or 2), or those observed outside the specified time frame. Exclusion considerations also encompass individuals with substantial missing data, patients subjected to treatments with significant impacts on survival outcomes.

All patients with prostate cancer who were observed and followed up from 1 January 1960 to 1 June 1966 made up the study population. 502 patients in a clinical study of those with stage 3 or stage 4 prostate cancer are included in the cross-sectional data, which include information on 15 variables, including treatment (estrogen doses), months of follow-up, follow-up status, age in years, body mass index, cancer stage, performance rating, and history of cardiovascular disease. Blood pressure readings in the systolic and diastolic ranges, an electrocardiogram, serum hemoglobin, Serum prostatic acid phosphatase, bone metastases, a combined index of stage and histologic grade, and size of primary tumors.

The variable status indicates if a patient is still alive, or the cause of death. Since we are not interested in distinguishing between causes of death in this instance, we create an indicator variable that shows whether a patient is alive or dead. The variable of interest, d time, which represents the number of months until death or censoring, can then be examined using this variable.

The data obtained was analyzed using R and SPSS. As the median is less impacted by outliers and skewed data, the Kaplan-Meier methodology was utilized to estimate survival rates, and the confidence interval method was used to determine the median survival time. Additionally, the null hypothesis that there is no difference in survival time was tested using the Log-Rank test to compare two or more groups. To investigate the association between variables and prostate cancer patient survival time, and to find the prognostic factors associated with prostate cancer based on the available data, the AFT models were fitted-this include: Exponential, Weibull, Lognormal, and Loglogistics. The AIC and Cox-Snell residual were used to check the goodness of fits of the models.

In this prostate cancer study, inclusion criteria encompass patients who have received a histological diagnosis of prostate cancer, ensuring diagnostic accuracy. The focus is on individuals with stage 3 (locally advanced) or stage 4 (metastatic) prostate cancer, acknowledging their potential for advanced disease management. Patient inclusion is restricted to those observed and diagnosed within a predefined time frame, promoting data consistency. Conversely, exclusion criteria pertain to patients with concurrent cancer diagnoses other than prostate cancer, early-stage prostate cancer (e.g., stage 1 or 2), or those observed outside the specified time frame. Exclusion considerations also encompass individuals with substantial missing data, patients subjected to treatments with significant impacts on survival outcomes.

RESULTS

In our study, the subject of analysis was the data from 502 patients with grade 3 or 4 prostate cancer that had the event (death) after hormone therapy. The data showed 19 missing observations (age-1, weight-2, tumour size-5, combined index of stage and hist. grade-11) which were estimated using recursive partitioning in R.

Results showed that 70.7% of the patients died, 29.3% were alive until study ended. Median survival time for patients was 35 months while overall survival rates for patients for 60-to-75 months were 31.7% and 23.2%.

Based the hormone therapy administered in different doses to prostate cancer patients, 1.0 mg estrogen dose significantly increases the chances of survival with 41.5 months for median survival rate of the patients as compared to 5.0 mg dose, 0.2 mg dose, and placebo with 35, 30 and 33 months respectively. It was found that, individuals with no bone metastasis had a median survival time of 37.5 months as against 21 months for those with bone metastasis. Also, individuals with no history of cardiovascular disease had 50% chance of surviving of 40 months and beyond. Furthermore, individuals with stage 3 cancer median survival time of 41 months while those with stage 4 had 29 months. Interestingly, individuals that are aged ≤55, 55, and ≥55-year, had a median survival time of 53 months, 49 months, and 34 months respectively.

Weibull AFT model turns out to be the best fit for our data, with AIC: 3469.032. The significant predictor variables for prostate cancer at 5% level of significance are: treatment-1.0 mg estrogen (hazard=1.447, p=0.007), age at diagnosis (hazard=0.983, p=0.015), weight index (hazard=1.009, p=0.011), size of primary tumour (hazard=0.986, p=0.000), history of cardiovascular disease (hazard=0.636, p=0.000), combined index of stage and histologic grade (hazard=0.940, p=0.015), and serum hemoglobin (hazard=1.060, p=0.036).

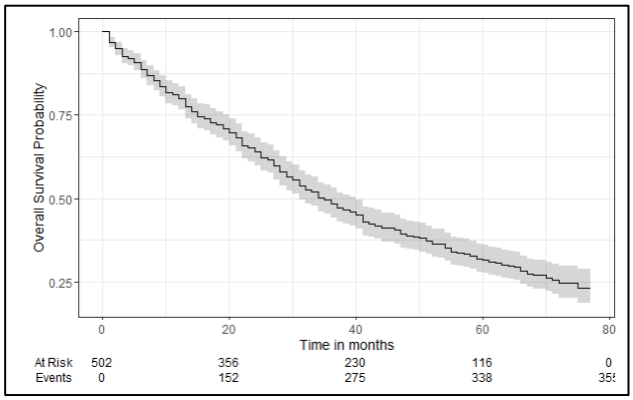

Figure 1: Overall survival probability and individuals at risk.

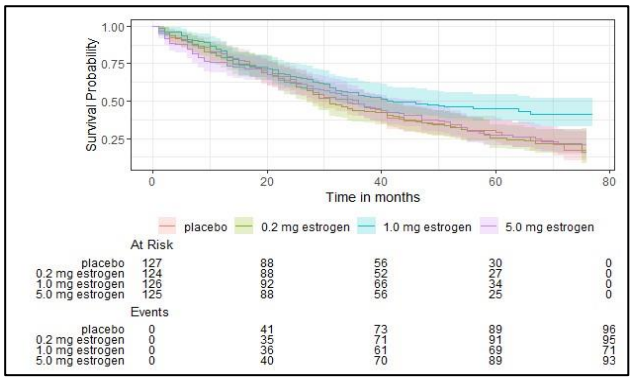

Figure 2: Survival curve for treatment types and risk table.

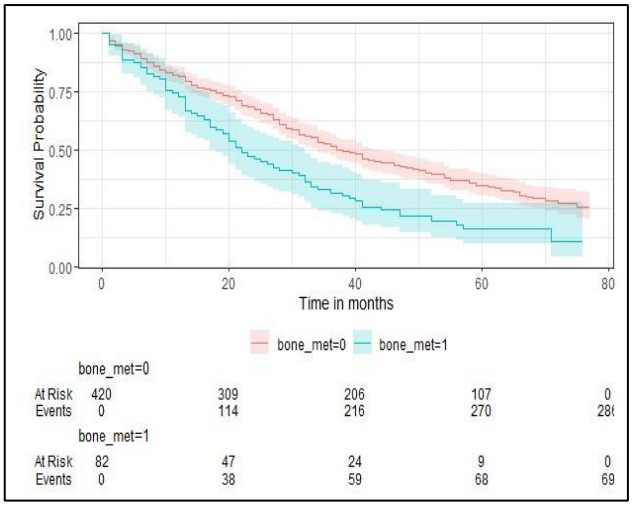

Figure 3: Survival curve for bone metastases and risk table (bone_met=0=no, 1=yes).

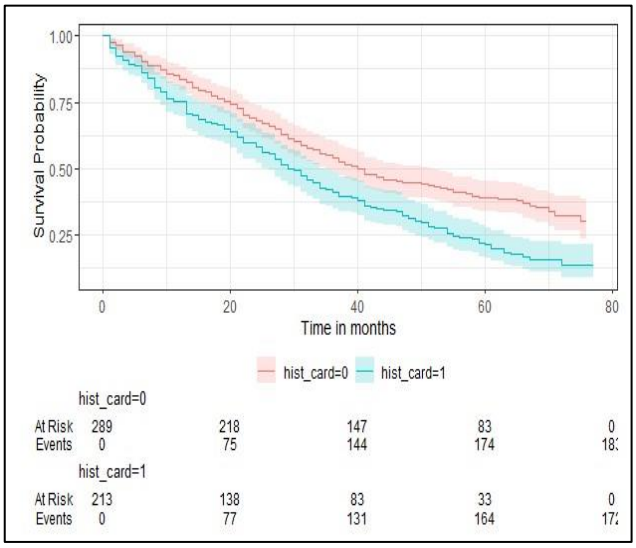

Figure 4: Survival curve for history of cardiovascular disease and risk table (hist_card=0=no, 1=yes).

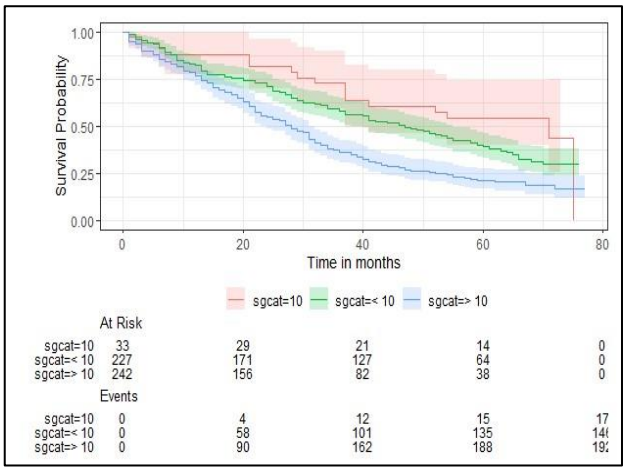

Figure 5: Survival curve for the combined index of stage and histological grade category and risk table.

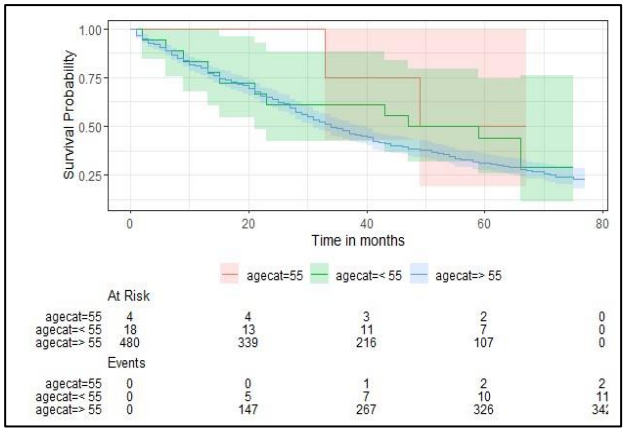

Figure 6: Age category and risk table.

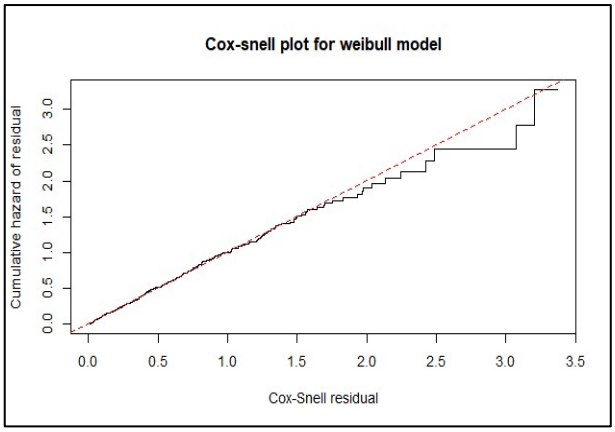

Figure 7: Cox-Snell residual plot for Weibull model.

Table 1: Kaplan-Meier estimates and median survival time of prostate cancer patients.

Factor	Median survival time (months)	Std. err	95% CI	Log rank test	
				Chi. sq	P value
Treatment					
Placebo	34	4.024	26.11-42.89	9.221	0.027
0.2 mg estrogen	31	2.582	25.94-36.06		
1.0 mg estrogen	41	9.228	22.91-59.09		
5.0 mg estrogen	36	3.008	30.11-41.90		
Overall	35	1.923	31.23-38.77		
Bone metastasis					
No	38	2.446	33.21-42.80	15.882	0.000
Yes	22	2.880	16.35-27.65		
Overall	35	1.923	31.23-38.77		
History of cardiovascular disease					
No	41	3.398	34.34-47.66	19.019	0.000
Yes	30	2.213	25.66-34.34		
Overall	35	1.923	31.23-38.77		
Age (In years)					
<55	47	15.972	15.69-78.31	1.906	0.386
55	49	NA	NA		
>55	34	2.103	29.87-38.12		
Overall	35	1.923	31.23-38.77		
Combined index of stage and histologic grade					
<10	47	4.068	39.03-54.97	26.669	0.000
10	71	16.147	39.35-102.65		
>10	28	2.067	23.95-32.05		
Overall	35	1.923	31.23-38.77		

Table 2: Weibull AFT model: predictors of survival for prostate cancer.

Factors	β Coeff.	Std. Err.	Haz. ratio	95% CI	P value
(Intercept)	4.395	0.812	81.045	79.45-82.64	0.000
0.2 mg estrogen	- 0.013	0.124	0.987	0.78-1.26	0.917
1.0 mg estrogen	0.364	0.136	1.440	1.10-1.88	0.008
5.0 mg estrogen	0.061	0.127	1.060	0.83-1.36	0.629
Age (In years)	- 0.018	0.007	0.983	0.97-1.00	0.015
Weight index	0.009	0.004	1.010	1.00-1.02	0.011
Bone metastases	- 0.236	0.139	0.789	0.60-1.04	0.088
Size of tumour (cm squared)	- 0.014	0.004	0.986	0.98-0.99	0.000
History of cardiovascular disease	- 0.452	0.094	0.636	0.53-0.77	0.000
Combined index of stage and histologic grade	- 0.062	0.026	0.940	0.89-0.99	0.015

Continued.

Factors	β Coeff.	Std. Err.	Haz. ratio	95% CI	P value
Blood pressure ratio (sdp/dbp)	0.059	0.139	1.060	0.81-1.39	0.671
Serum prostatic acid phosphatase	0.000	0.001	1.000	1.00-NA	0.563
Serum hemoglobin (gr/100 ml)	0.055	0.026	1.060	1.00-1.11	0.036
Log (scale)	- 0.167	0.045	0.846	0.76-0.93	0.000

Loglik (model)=-1720.5, Loglik (intercept only)=-1766.4, Chi sq.=91.82 on 12 degrees of freedom, p=0.000

DISCUSSION

Prostate cancer is the most prevalent and lethal cancer in males worldwide. Using survival analysis, studies have shown the long term overall performance of a group of patients diagnosed or treated and are under study for a period of time. This study is carried out to determine the median survival time, the prognostic factors for prostate cancer, and fit an AFT model that explains best the data.

This study showed that, the overall median survival time for prostate cancer patients based on the independent variables analyzed was 35 months. However, patients administered 1.0 mg estrogen had five-year survival rate of 44.9% as compared to 25.3%, 27.4%, and 29.5% for those administered 0.2 mg estrogen, 5.0 mg estrogen, and Placebo respectively. The type of treatment can influence a patient's status after diagnosis, there was significant evidence to show that the treatment type 1.0 mg estrogen dose was a major prognostic factor (p=0.08) which increases patients' survival rate more than one time the other treatment types.

Patients with no bone metastasis had five-year survival rate of 34.6%, and 16.1% for patients with bone metastasis and there exist a significant difference in this survival rate (p=0.000). This contradicts the result by Shamsul, A. et al with 57% survival rate for patients with metastasis.[4] While Nesbit reported that the average survival of prostate cancer patients with bone metastases was between 1 and 176 months, with the longest surviving patient having survived for 15 years. He also pointed out that for patients with cancer metastases during diagnosis, the opportunity to cure was impossible.[6] A study in a university hospital in Malaysia on a seven-year follow-up reported a median survival rate for patients with metastasis of 32.6 months, whereas a survival mean of 38.1 months for patients with metastasis was reported in Thailand with a one-year survival rate of 78.8%.[7,8] However, in this study, bone metastasis was not a significant prognostic factor for prostate cancer (p=0.088) at 5% level of significance.

Cardiovascular disease has been seen as a leading cause of mortality in patients with prostate cancer, and combining androgen deprivation therapy (ADT) may worsen cardiovascular risk.[9] This study has demonstrated a significant difference in survival times (p=0.000) of prostate cancer patients with history of cardiovascular disease and those with no history of cardiovascular disease. The study went further to show that there is a significant impact of the history of cardiovascular disease on survival rate of prostate cancer patients (p=0.000). Patients with history of cardiovascular disease clearly have a much lower survival probability (Table 2).

The combined index of stage and histologic grade was categorized in to three; index <10, index =10, index>10. We see from the results that, the survival probability is increased when the index is equal 10. This is evidence from the median survival times of 71 months, 47 months, and 28 months for index =10, index <10, and index > 10, respectively. The result in Table 2 further showed that, combined index of stage and histological grade is a significant prognostic factor for prostate cancer. However, the impact on survival probability is negative.

This study found out that most of the patients who came for the treatment were older than 55 years (95.6%). And based on the age categorization (<55, =55, and >55), there was an insignificant difference (p=0.386) in the median survival times (Table 1). Age was one of the predictive factors in this study for patients with prostate cancer. As the patients get older, the probability of survival is significantly (p=0.015) decreased by almost one time when they are younger. Similar conclusion was drawn from a study in Iran that examined 113 patients' survival data and found that patient age at diagnosis was a significant predictor of prostate cancer survival (p=0.05).[10] The rate of survival is frequently influenced by other factors, such as concomitant conditions and cancer-related factors, therefore the age factor alone cannot be explained as a predictor. This is in line with research by Bechis et al. and Subahir et al which found that age affected the survival rate for prostate cancer and that patients over 75 were likely to receive less aggressive treatment due to their weakened body physiology. Their research showed that men diagnosed with prostate cancer beyond the age of 70 have a 52.1% higher risk of having the disease at an advanced stage compared with 33.0% risk of men diagnosed with prostate cancer before the age of 60.[11,12]

In the present study, weight index, tumour size, and serum hemoglobin were also significant prognostic factors of prostate cancer. Where weight index has shown an increased likelihood of survival which indicates that most of the patients have normal body weight. In a meta-analysis, a significant difference was observed between the obese and normal weight (p<0.001) and 54% of obese has a risk compared to normal weight. The study went further to conclude that obesity is associated with a higher risk of death from prostate cancer.

The study's drawbacks encompass several aspects. Firstly, it hinges on information extracted from a 1980

publication, which might not precisely reflect the present state of medical practices and the demographics of prostate cancer patients. Secondly, the analysis focused on 15 variables, potentially missing out on other crucial factors that could influence the survival of prostate cancer patients. Furthermore, the exclusive use of a single data source might introduce a bias in the selection of data.

CONCLUSION

In conclusion, the median survival time for prostate cancer patients was found to be 35 months. The best fit AFT model was Weibull model with AIC: 3469.032. Hence, the significant prognostic factors for prostate cancer at 5% level of significance were treatment-1.0 mg estrogen, age at diagnosis, weight index, size of tumour, history of cardiovascular disease, the combined index of stage and histological grade, serum hemoglobin. To increase the survival rate of prostate cancer patients in Africa and the world at large, preventative measures such prostate cancer screening, early identification, and early treatment should be done. The focus should be on raising awareness about prostate cancer among adolescents through school health programs, and providing easily accessible and reasonably priced diagnostic and treatment options at the level of primary health care.

The findings of this study should help with understanding and managing prostate cancer patients as well as with developing more effective future plans to increase their chances of survival and quality of life.

ACKNOWLEDGEMENTS

Author would like to appreciate Byar D. P. and Green S. B. through which the data was made available after the multivariate study group of the royal statistical society and we would like to express my thanks to Agnes Herzberg for making this possible. The authors appreciatethe efforts of the anonymous reviewers toward this publication.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Piñeros M et al Global Cancer Observatory: cancer today. Lyon (France). International Agency for Research on Cancer. 2018. Available at: https://gco.iarc.fr/today/home. Accessed on 08 August, 2023.
2. Chidebe RCW, Orjiakor CT, Pereira I, Ipiankama SC, Lounsbury DW, Moraes FY. Navigating prostate cancer control in Nigeria. Lancet Oncol. 2019;20(11):1489-91.
3. Howlader AMN, Krapcho M, Neyman N, Aminou R SEER Cancer Statistics Review, 1975-2008, National Cancer Institute, Bethesda, Md, USA, 2011. Available at: http://seer.cancer.gov/csr/19752008/. Accessed on 08 August, 2023.
4. Shamsul A, Norzaher I, Syafiq T, Siti NM, Nazarudin S. Survival Analysis and Prognostic Factors for Prostate Cancer Patients at Universiti Kebangsaan Malaysia Medical Centre, Kuala Lumpur. Sains Malaysiana. 2021;50(5):1367-79.
5. Singh R, Mukhopadhyay K. Survival analysis in clinical trials: Basics and must know areas. Perspectives Clin Res. 2011;2(4):145-8.
6. Nesbit RM. Prostatic carcinoma: A follow-up on 795 patients treated prior to the endocrine era and a comparison of survival rates between these and patients treated by endocrine therapy. Surgery. 1946;20:263-72.
7. Hong GE, Kong CH, Singam P, Cheok LB, Zainuddin ZM, Azrif M. Seven-year review of prostate carcinomas diagnosed by TRUS biopsy in a single Malaysian institution. Asian Pacific J Cancer Prevent. 2010;11(5):1351-3.
8. Phanphaisarn A, Patumanond J, Settakorn J, Chaiyawat P, Klangjorhor J. Prevalence and survival patterns of patients with bone metastasis from common cancers in Thailand. Asian Pacific J Cancer Prevent. 2016;17(9):4335-40.
9. Lova S, Ravi BP, Rebecca AH, John C, Samuel UT, David JV et al. Assessment and Management of Cardiovascular Risk Factors Among US Veterans with Prostate Cancer. 2021;4(2):e210070.
10. Zahir ST, Nazemian MR, Zand S, Zare S. Survival of patients with prostate cancer in Yazd, Iran. Asian Pacific J Cancer Prevent. 2014;15(2):883-6.
11. Bechis SK, Carroll PR, Cooperberg MR. Impact of age at diagnosis on prostate cancer treatment and survival. J Clin Oncol. 2011;29(2):235-41.
12. Subahir MN, Shah SA, Zainuddin ZM. Risk factors for prostate cancer in Universiti Kebangsaan Malaysia Medical Centre: A case-control study. Asian Pacific J Cancer Prevent. 2009;10(6):1015-20.

Cite this article as: Sule GI, Chukwu AU, Akanno FC. Accelerated failure time survival model for prostate cancer. Int J Community Med Public Health 2023;10:3459-64.