Bayesian survival analysis of time-to-remission of prostate cancer and associated prognostic factors in a health-based institute, South-West Nigeria

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Abstract

Background: Prostate cancer (CaP) develops when healthy cells in the prostate gland change and grow out of place, forming a tumour. In Nigeria, this disease is on an upward trajectory, despite the availability of screening services. This study seeks to estimate the time-to-remission and to determine the prognostic factors for prostate cancer remission.

Method: A retrospective analytical study design was employed, through the extraction of case files of patients diagnosed and treated for CaP from January 2010 to December 2017 at the University College Hospital, Ibadan. The extracted data were further divided into two cohorts 2010 to 2014 and 2015 to 2017 to account for non-treatment months. Kaplan Meier method was used to estimate the time-to-remission. Bayesian parametric (Weibull) Accelerated Failure Time (AFT) model was used to determine the factors associated with time-to-remission.

Results: The average age(SD) of the patients was 72(3.65) years, with peak incidence among those aged 70 – 79 years. Most CaP patients (87.3%) were diagnosed at stage IV, with many having metastasis to the spine. Among the patients, (33.6%) received chemotherapy and surgery. Patients from Northcentral part of Nigeria had the highest Median Time to Remission (MTR) of 3.7 months in the (2015 - 2017) cohort. The MTR for the 2010 - 2014 cohort was 2.9 months, 3.3 months for the 2015 - 2017 cohort while the overall MTR for the study was 3.2 months. Ages 60 – 69 years and 79 years and above in the 2010 – 2014 cohort decelerated time-to-remission by 30% (adjusted Time Ratio (aTR) = 1.3; 95% CrI (Credible Interval): 1.1 – 1.5) and 40% (aTR = 1.4; 95% CrI: 1.1 – 1.8) respectively. Time-to-remission was significantly delayed by 40% (aTR = 1.4; 95% CrI: 1.1 – 1.7), and 230% (aTR = 3.3; 95% CrI: 2.1 – 4.9) for patients from the south-south and north-central respectively for the 2015 – 2017 cohort compared to patients from the south-west.

Conclusion: We found that patients age, location, marital status, occupation, stage, method of diagnosis, Gleason group, site and treatment received significantly influence the time to CaP remission. Stakeholders should therefore sensitize men well advanced in age to take up regular prostate examination as well as emphasize early presentation.

Background

The Prostate is a walnut-sized organ located just between the bladder and the male reproductive organ, and it slowly grows larger to an average weight of 40 grams in ageing men [1, 2]. A prostate gland surrounds the urethra that empties urine from the bladder and also secretes prostate fluid that protects sperm [3, 4]. These physiological functions may be compromised during various prostate diseases including prostatitis, benign prostatic hyperplasia, and cancer [5, 6]. Prostate cancer (CaP) develops when healthy cells in the prostate gland change and grow out of place, forming a mass called a tumour [4, 7]. Pathologic evidence suggests that neoplastic changes of the prostate epithelium develop early in a man's adult life, but do not become clinically evident or problematic until decades later. Some patients live out their lives with prostate cancer that remains stable for decades without treatment. In other cases, CaP grows aggressively, responds poorly to therapy, and causes death within a few years [8, 9]. According to Global Cancer Statistics 2018, lung cancer is the leading cause of cancer death (18.4% of the total cancer deaths), followed by female breast cancer (11.6%), and prostate cancer (7.1%) been third in the hierarchy [10]. Prostate cancer is the second most common and fifth-most aggressive neoplasm among men worldwide[2, 10].

About three-quarters of CaP cases worldwide occur in men aged 40 years and above with increasing incidence and morbidity in men of black African ancestry [11–13]. In 2012, 1.1 million men were diagnosed with CaP and 70% of them (795,000 cases) were in developed countries [9, 14]. A CaP lifetime prevalence of one in seven men in the US and one in 25 globally have been reported [10, 15]. Available reports indicate that CaP accounts for approximately 20.3% and 4.8% of all male cancers in sub-Saharan Africa and North Africa, respectively [11, 16]. CaP is on the upward trajectory among Nigerian men and remains one of the most common cancers among men in this region [17]. A CaP prevalence rate of 1046 per

100,000 men of age > 40years screened was reported in Lagos, Nigeria [18, 19]. Compared to African-American men, Nigerian men are 10 times more likely to have prostate cancer and 3.5 times more likely to die from it [18–20].

Environmental, clinic-pathological factors and most importantly treatment regimen, have been incriminated as the reason for geographic variations in incidence and mortality [9, 14]. Studies have reported that the main risk factors of CaP are age, inheritance known as race and/or family history, smoking, benign prostatic hypertrophy (BPH) and diet [2, 21–25]. CAP has been reported to be more prevalent among older people, those with poorer diet, having animal fat and/or dairy products or smokers. The chance of having prostate cancer rises rapidly after age 50 [21, 22]. About 60% of prostate cancer are found in men older than 65 years [22]. In particular, the American Cancer Society affirmed that CaP develops more often in African-American and African-Caribbean men more than in men of other races in the world [22]. Some studies have demonstrated an association between BPH and prostate cancer, while others have not [21, 22]. While some studies have explored stages at the presentation of CaP and explored associated risk factors in Nigeria using statistical frequentist approaches, we are not aware of any study that combined robust methods such as Bayesian statistics and survival analysis to assess prognostic factors of Cap in Nigerian. Hence, this study seeks to estimate the time to remission and to determine the prognostic factors for prostate cancer remission among people seeking care at a Nigerian tertiary health facility using a Bayesian survival analysis method.

Materials And Methods

Study design

A retrospective analytical study design was employed. This was done through a review and extraction of hospital records. The case files of all patients diagnosed and treated for prostate cancer from January 2010 to December 2017 at the University College Hospital (UCH) Ibadan were included in the study.

Study setting

The study site was the Department of Radiation Oncology, University College Hospital, Ibadan, Nigeria. The facility serves as a referral centre for secondary health facilities in the southern part of Nigeria. It is one of the leading facilities for the management of different types of cancer in Nigeria [26]. The hospital has over 500-bed spaces and has been used for the study of cancer survivorship in Nigeria [26].

Study Population

This study consists of all Prostate cancer patients who were managed for prostate cancer at the University College Hospital, Ibadan from January 2010 to December 2017.

Data Collection Procedure

A proforma was used to extract relevant data from patients' records, with the assistance of medical record clerks. The extracted data were divided into two cohorts 2010 – 2014 and 2015 – 2017 to account for non-treatment months. A total of 354 patients with 90% of required records was extracted. 110 experienced remission, while 54 were censored in the 2010–2014 cohort. Also, in the 2015-2017 cohort, 115 patients experienced remission, while 75 were censored; with a follow-up time of 15 months observed in each cohort. To ensure data reliability, the extracted records were cross-checked by a radiotherapist. All methods were carried out in accordance with relevant guidelines and regulations.

Study Variables

Dependent variable: The dependent variable was the time to remission measured in months from time of presentation to time patient was last seen. A patient or an individual is declared to have experienced remission when they become prostate cancer-free or have no residual disease on medical examination after completion of treatment. Meanwhile, patients that were either still under follow-up, lost to follow-up, death from CaP without having remission or other diseases were censored. Independent variables: The independent variables for this study include patients' socio-demographics and clinical characteristics.

Data Analysis

Descriptive statistics such as frequency, proportions, the mean and standard deviation were used to describe the patient's socio-demographic characteristics, clinical characteristics and treatment modality. Kaplan-Meier method was used to estimate the time-to-remission. Bayesian parametric (Weibull) Accelerated Failure Time (AFT) model was used to determine the factors associated with time-to-remission. This approach has been reported to perform better than the frequentist approach and the Cox semi-parametric models in the literature [27, 28]. STATA version 15 was employed in the analysis. All statistical tests were two-tailed with a 5% significance level.

Estimation of time-to-remission

Due to the presence of right-censored data, the Kaplan-Meier method was used to assess survivorship in this study.

Suppose we have p distinct survival times arranged in increasing order, say $t_1 < t_2 < \dots < t_p$. Wherein, at time t_i there are n_i subjects who are said to be at risk i.e. they survived up to this time and were not censored. The number of subjects who failed at time t_i is denoted by d_i . Consider the recursive equation

$$\begin{aligned} S(t_i) &= \{ \text{rm P} \} (T > t_i) = \{ \text{rm P} \} (T > t_i | T > t_{i-1}) * \{ \text{rm P} \} (T > t_{i-1}) \\ &= \{ \text{rm P} \} (T > t_i | T > t_{i-1}) * S(t_{i-1}), i = 1, \dots, p. \end{aligned}$$

Where $t_0 = 0$ and $S_0 = 1$

Therefore, the survival function is given as

$$s(t) = S'(t) = \frac{d}{dt} S(t) = \frac{d}{dt} \int_t^{\infty} f(u) du = \frac{d}{dt} [1 - F(t)] = -f(t)$$

The survival time t is the period (months) to remission, from time of diagnosis to time last treated/seen, since all patients are at risk of this event. The censoring index for patients who experienced remission is "1" whereas patients who are still undergoing treatment, died from CaP or a disease other than CaP, patients who can no longer be observed (Loss-to-follow-up), are declared censored and coded as "0".

Bayesian Parametric (Weibull distribution) Accelerated Failure Time model

Bayesian analysis generates conclusions based on the synthesis of new information from the observed data and previous knowledge or external evidence. The Weibull model is one of the accelerated failure time models that can be used to fit

survival data under the Bayesian framework. It was adopted in this study as it fitted the data more than other parametric models. The accelerated failure time implies a deceleration of time or, in other terms, an increment in the expected waiting time for an event of interest to occur.

Let t_i denote the survival time of the i^{th} patient. Assuming that t_i has a Weibull distribution with space and shape parameters $\alpha > 0$ and $r > 0$, having a density function of the form:

$$f(t_i|\alpha, r) = \alpha t_i^{\alpha-1} \exp(-[rt_i]^\alpha), \quad 0 < t_i < \infty.$$

The survival function of t_i is given by

$$S(t_i|\alpha, r) = \exp(-\exp(rt_i)^\alpha t_i).$$

The hazard function is given by

$$h(t_i|\alpha, r) = r\alpha t_i^{\alpha-1}.$$

The likelihood function of the unknown parameters (α, r) given the data can be written as:

$$L(\alpha, r|D) = \prod_{i=1}^n f(t_i|\alpha, r) S(t_i|\alpha, r)^{(1-\delta_i)}$$

$$= \exp \left\{ r \sum_{i=1}^n \delta_i + \sum_{i=1}^n \delta_i (a-1) \log(t_i) - \exp(r) t_i^\alpha \right\},$$

[29–32]

where δ_i is an indicator variable taking value 1 if t_i is the failure time (i.e time-to-remission) and 0 if t_i is right censored (loss-follow-up, death, still under follow up).

To incorporate covariates we, therefore, write $r = X'_i \beta$, where X'_i and β are $p \times 1$ vector of covariates and regression coefficients respectively.

Assuming a normal prior for β , $N_p(\mu_0, \Sigma_0)$ then the joint posterior is given by

$$\prod (\beta, \alpha|D)^\alpha \alpha^{\alpha_0+d+1} \exp \sum_{i=1}^n (\delta_i + X'_i \beta + \delta_i(\alpha-1) \log(t_i)) - t_i^\alpha \exp(X'_i \beta) - k_0^\alpha \quad 1.6$$

$$- \frac{1}{2} (\beta - \mu_0) \Sigma_0^{-1} (\beta - \mu_0),$$

where $D = (n, t, X, \delta)$ denote the observed data for the regression model and X is an $n \times p$ matrix of covariates with the i^{th} row as X'_i and $\delta = (\delta_1, \dots, \delta_n)'$.

The “bayes”, “streg”, and “tr” packages in STATA 15 was used to fit the Bayesian AFT model using the random-walk Metropolis-Hastings Monte Carlo Markov Chain (MCMC) sampling method for simulating the results of the parameters. For each covariate in the model, a Time Ratio (TR) > 1 implies that an individual experienced the event at a later timing, TR = 1 suggest no difference in the timings, while TR < 1 suggest an earlier timing.

The Metropolis-Hastings algorithm is given as follows:

Let $q(\theta, \vartheta)$ be a proposal density which is also termed as a candidate generating density such that

$$\int q(\theta, \vartheta) d\vartheta = 1$$

Also, let $\mu(0,1)$ denote the uniform distribution over (0,1). Then, a general version of the Metropolis-Hastings algorithm for sampling from the posterior distribution $P(\theta|x)$ can be described as follows:

Step 0. Choose an arbitrary starting point θ_0 and set $i = 0$.

Step 1. Generate a candidate point θ^* from $q(\theta_i, \cdot)$ and u from $\mu(0,1)$

Step 2. Set $\theta_{i+1} = \theta^*$ if $u \leq a(\theta_i, \theta^*)$ and $\theta_{i+1} = \theta_i$ otherwise, where the acceptance probability is given by

$$a(\theta, \vartheta) = \min \left\{ \frac{\pi(\vartheta|D)q(\theta, \vartheta)}{\pi(\vartheta|D)q(\theta, \vartheta)}, 1 \right\}.$$

Step 3. Set $i = i + 1$, and go to Step 1.

The iteration steps from 0 through 3 is referred to as an MH update. By design, any Markov chain simulated using this MH algorithm is guaranteed to have the posterior distribution as its stationary distribution.

Criteria's for measuring the efficiency of MCMC are the acceptance rate of the chain and the degree of autocorrelation in the generated sample. When the acceptance rate is close to “0” then most of the proposals are rejected, which means that the chain failed to explore regions of the appreciable posterior probability. The cut-off for acceptance rate is 0.234 for a multivariate posterior and 0.45 for a univariate posterior. The -2loglikelihood, Bayesian Information Criterion and Deviance Information Criterion (DIC) were also used to evaluate model performance.

Results

Distribution of prostate cancer (CaP) patients by sociodemographic characteristics

Three hundred and fifty-four patients were aged 50 – 104 years, with an average age of 72years and a standard deviation of 9.52. Patients 50 – 59 years were 33(9.3%), 60 – 69 years 90(25.4%) The peak incidence of CaP was observed among those age 70 – 79 years 141(39.8%) while those 79 years above were 90(25.4%). Those married were 347(97.7%), 8(2.3%) were widowers, 181(51.1%) civil servants, 4(1.1%) unemployed, 9(2.5%) farmers and 16(4.5%) were factory workers and others (taxi drivers, artisans, labourers, businessmen) 144(40.7%) as shown in Table 1.

Table 1
Distribution of prostate cancer patients by sociodemographic characteristics

Characteristics	n	%
Age (years) Mean(SD)	70(3.65)	
50 – 59	33	9.3
60 – 69	90	25.4
70 – 79	141	39.8
79 – above	90	25.4
Marital Status		
Currently married	346	97.7
Widower	8	2.3
Occupation		
Civil Servant	181	51.1
Farming	9	2.5
Factory Worker	16	4.5
Unemployed	4	1.1
Others	144	40.7
Religion		
Christian	257	72.6
Islam	94	26.6
Others	3	0.8
Geographical Location		
South-west	278	78.5
South-south	38	10.7
South-east	30	8.5
North-central	8	2.3
Family History of Prostate Cancer		
Yes	77	21.8
No	277	78.2
Year of Diagnosis		
2010 - 2014	164	46.3
2015 – 2017	190	53.7
Co-morbidities		
<i>Others include: taxi drivers, artisans, labourers, businessmen</i>		

Characteristics	n	%
Alcohol and Tobacco	167	33.0
Coronary Artery	101	20.0
Diabetes	118	23.3
Hypertension/Stroke	120	23.7
Total	354	100.0
<i>Others include: taxi drivers, artisans, labourers, businessmen</i>		

Distribution of CaP patients by clinical characteristics

Of the 354 patients we studied, 193(54.5%) were diagnosed via Digital Rectal Examination (DRE), Biopsy 98(27.7%), and 20(5.6%) by Prostate-Specific Antigen (PSA) test. Patients with a poorly differentiated Gleason score were 220(62.1%), while 72(20.3%) were well differentiated. The majority, 309(87.3%), were diagnosed at stage IV while 11(3.1%) were diagnosed at stage I. Only one in 20 patients, 18(5.1%), had metastasis to the lymph node, 55(15.5%) rectum, 84(23.7%), while about a quarter had multiple metastases 81(22.9%).

Surgery was carried out on 67(18.9%) patients, while 42(11.9%) and 62(17.5%) received radiotherapy and chemotherapy respectively. About 14% had radiotherapy and surgery while 48(13.6%), chemotherapy and radiotherapy, while 9(2.5%) received all the three combinations of chemotherapy, surgery and radiotherapy. Of the total records extracted during this period, 225(55.6%) experienced remission after treatment, 17(10.2%) died from prostate cancer, 75(25.0%) were still under follow-up, while 37(9.2%) were lost to follow-up (Table 2).

Table 2
Distribution of prostate cancer patients by clinical
characteristics and treatments

Characteristics	n	%
Method of Diagnosis		
PSA test	20	5.6
DRE test	193	54.5
Transrectal Ultrasound	9	2.5
Biopsy	98	27.7
DRE & Biopsy	34	9.6
Gleason group		
Well-differentiated	72	20.3
Moderately differentiated	62	17.5
Poorly differentiated	220	62.1
Stage at Diagnosis		
Stage I	11	3.1
Stage II	12	3.4
Stage III	12	3.4
Stage IV	309	87.3
Unknown	10	2.8
Site of Metastasis		
Lymph node	18	5.1
Rectum (bladder neck)	55	15.5
Bones	84	23.7
Spine	116	32.8
Multiple Metastasis	81	22.9
Treatment Modality		
Surgery alone	67	18.9
Radiotherapy alone	42	11.9
Chemotherapy alone	62	17.5
Radiotherapy & Surgery	7	2.0
Chemotherapy & Radiotherapy	48	13.6
Chemotherapy & Surgery	119	33.6
Chemotherapy & Surgery & Radiotherapy	9	2.5
Treatment Outcome		

Characteristics	n	%
Disease-free	225	55.6
Death from Prostate cancer	17	10.2
Still under follow-up	75	25.0
Loss-to-follow up	37	9.2
Total	354	100.0

Median Time-to-Remission of socio-demographic and clinical characteristics among CaP patients

The result showed that a total of 354 patients were diagnosed and treated for CaP between 2010 – 2017, with a maximum follow-up time of 15 months observed for all patients. Of the 164 patients in the 2010 – 2014 cohort, 110 experienced remission, while 54 were censored. Among the 190 patients in the 2015 – 2017 cohort; 115 experienced remissions, while 75 were censored. It was observed that patients aged 50 – 59 years in the 2010 – 2014 cohort had a Median Time-to-Remission (MTR) of 3.5 months while those in the 2015 – 2017 cohort had an MTR of 3.8 months, patients aged 60 – 69 years in the 2010 – 2014 cohort had an MTR of 4.2 months; meanwhile patients aged 79 years and above had a median time-to-remission of 2.2 months in the 2010 – 2014 cohort (Table 3).

Among patients with no family history of prostate cancer, time-to-remission was 3.1 months, while it was 2.9 months for patients in the well-differentiated Gleason group and 3.3 months for patients in the poorly differentiated Gleason group. Time-to-remission was 2.3 months for patients diagnosed at stage I and 3.3 months for patients diagnosed at stage II and IV respectively.

Time-to-remission for patients who underwent surgery among the 2010 – 2014 cohort was 1.6 months and 2.4 for those in the 2015 – 2017 cohort as shown in Table 3 and Figure 1. The overall median time-to-remission was 2.2 months, while those who received radiotherapy alone time-to-remission was one and a half months after treatment. The time-to-remission among those treated with the combination of radiotherapy and surgery was 4.6 months while those treated with a combination of chemotherapy and surgery was more than five months in the 2010 - 2014 cohort as shown in Table 3.

Table 3
Median Time-to-Remission among prostate cancer patients

Characteristic	2010 – 2014		2015 - 2017		Overall	
	n	MTR	n	MTR	n	MTR
Age						
50 – 59	15	3.5	18	3.8	33	3.5
60 – 69	44	4.2	46	2.9	90	3.6
70 – 79	69	2.7	72	3.4	141	2.9
79 – above	36	2.2	54	3.4	90	2.8
Marital Status						
Currently married	160	2.8	186	3.3	346	3.2
Widower	4	0.7	4	0.9	8	0.9
Occupation						
Civil Servant	92	2.6	89	3.0	181	2.9
Farming	3	1.8	6	2.8	9	2.8
Factory Worker	9	5.2	7	4.5	16	5.1
Unemployed	3	1.1	1	CBC	4	1.2
Others	57	3.5	87	3.3	144	3.3
Religion						
Christian	121	2.9	136	3.3	257	3.2
Islam	41	2.5	53	3.4	94	2.7
Others	2	1.8	1	CBC	3	3.7
Geographical Location						
South-west	132	2.9	146	3.3	278	3.1
South-south	18	1.5	20	4.9	38	2.6
South-east	10	3.5	20	3.3	30	3.3
North-central	4	2.5	4	14.2	8	3.7
Family History of Prostate Cancer						
Yes	35	3.5	42	2.4	77	2.8
No	129	2.9	148	3.5	277	3.1
Method of diagnosis						
PSA test	10	3.1	10	2.8	20	2.9
DRE test	90	2.9	103	3.8	193	3.5

NB: CBC = can't be computed; Overall = 2010 – 2017

Characteristic	2010 – 2014		2015 - 2017		Overall	
Transrectal Ultrasound	5	2.3	4	0.6	9	1.4
Biopsy	44	2.9	54	2.9	98	2.9
DRE & Biopsy	15	2.6	19	4.2	34	2.7
Gleason group						
Well differentiated	32	1.9	40	4.7	72	2.9
Moderately differentiated	32	3.2	30	3.0	62	3.0
Poorly differentiated	100	3.5	120	3.3	220	3.3
Stage at Diagnosis						
Stage I	6	2.4	5	3.0	11	2.3
Stage II	6	2.1	6	3.5	12	3.3
Stage III	8	1.4	4	1.6	12	1.6
Stage IV	137	3.1	172	3.4	309	3.3
Unknown	7	3.5	3	1.5	10	3.5
Site of Metastasis						
Lymph node	6	2.3	12	4.3	18	3.5
Rectum (bladder neck)	22	3.1	33	4.0	55	3.5
Bones	41	2.4	43	2.9	84	2.7
Spine	56	2.6	60	3.3	116	2.9
Multiple Metastasis	39	4.2	42	3.0	81	3.4
Treatment Modality						
Surgery alone	29	1.6	38	2.4	67	2.2
Radiotherapy alone	22	1.5	20	3.2	42	2.6
Chemotherapy alone	28	2.9	34	2.7	62	2.9
Radiotherapy & Surgery	3	4.6	4	6.9	7	6.9
Chemotherapy & Radiotherapy	24	1.7	24	4.0	48	3.7
Chemotherapy & Surgery	56	5.9	63	4.4	119	4.6
Chemotherapy & Surgery & Radiotherapy	2	1.9	7	CBC	9	CBC
Overall	164	2.9	190	3.3	354	3.2
NB: CBC = can't be computed; Overall = 2010 – 2017						

Bayesian Weibull Accelerated Failure Time model analysis

In Table 4 the result of the multivariate Bayesian Weibull Accelerated Failure Time model showed that CaP patients aged 60 – 69 years and 79 years and above in the 2010 – 2014 cohort decelerate time-to-remission by 30% (adjusted Time Ratio (aTR) = 1.3; 95%CrI: 1.1 – 1.5) and 40% (aTR = 1.4; 95%CrI: 1.1 – 1.8) respectively. Widowers experienced a shorter time-to-remission by 70% (aTR = 0.3; 95%CrI: 0.2 – 0.3), 80% (aTR = 0.2; 95%CrI: 0.1 – 0.3), and 70% (aTR = 0.3; 95%CrI: 0.2 – 0.4) for the 2010 - 2014, and 2015 – 2017 cohorts and overall respectively compared to patients who were currently married. The time-to-remission decelerated more than twice for patients who were factory workers for the 2015 – 2017 cohort (aTR = 2.9; 95%CrI: 1.7 – 4.7).

Meanwhile being unemployed accelerated time-to-remission by 40% for the 2010 – 2014 cohort (aTR = 0.4; 95%CrI: 0.4 – 0.4) compared to patients who were civil servants. Time-to-remission was significantly delayed by 40% (aTR = 1.4; 95% CrI: 1.1 – 1.7) and 230% (aTR = 3.3; 95% CrI: 2.1 – 4.9) for patients from the south-south and north-central respectively for the 2015 – 2017 cohort compared to patients from the south-west. Patients in the poorly differentiated Gleason group experienced a delayed time-to-remission (aTR = 1.7; 95%CrI: 1.3 – 2.2) as compared to a well differentiated Gleason group (Table 3).

Metastasis to the bones and spine significantly delayed time-to-remission (aTR = 1.5; 95%CrI: 1.1 – 2.1) and (aTR = 1.3; 95%CrI: 1.1 – 1.6) respectively as compared to metastasis to the lymph node. Having treatment by radiotherapy and a combination treatment of chemotherapy, surgery and radiotherapy significantly accelerated time-to-remission by 30% (aTR = 0.7; 95%CrI: 0.7 – 0.8) and 50% (aTR = 0.5; 95%CrI: 0.4 – 0.8) respectively as shown in Table 4. the MCMC convergence diagnostics for stage at diagnosis among the 2010 – 2014 and 2015-2017 cohorts are shown in Figures 2 and 3 respectively.

Table 4
Adjusted determinants of prostate cancer survivorship using Bayesian Parametric (Weibull Distribution) Regression model

Characteristic	2010 – 2014	2015 - 2017	Overall
	aTR(95%CrI)	aTR(95%CrI)	aTR(95%CrI)
Age			
50 - 59	1.0	1.0	1.0
60 - 69	*1.3(1.1 – 1.5)	1.3(0.4 – 2.8)	0.9(0.8 – 1.2)
70 – 79	1.1(0.8 – 1.4)	1.3(0.5 – 2.2)	0.9(0.8 – 1.2)
79 - above	*1.4(1.1 – 1.8)	1.9(0.7 – 3.5)	0.9(0.7 – 1.3)
Marital Status			
Married	1.0	1.0	1.0
Widower	0.3(0.2 – 0.3)*	0.2(0.1 – 0.3)*	0.3(0.2 – 0.4)*
Occupation			
Civil Servant	1.0	1.0	1.0
Farming	0.8(0.6 – 1.1)	1.0(0.8 – 1.4)	1.1(0.5 – 1.8)
Factory Worker	2.1(1.3 – 3.2)*	2.9(1.7 – 4.7)*	1.9(1.0 – 3.1)*
Unemployed	0.4(0.4 – 0.4)*	1.0(0.7 – 1.4)	0.6(0.4 – 1.6)
Others	0.8(0.7 – 0.8)*	1.2(0.9 – 1.5)	0.9(0.7 – 1.3)
Religion			
Christian	1.0	1.0	1.0
Islam	0.8(0.7 – 0.9)*	0.8(0.7 – 1.2)	0.9(0.7 – 1.3)
Others	0.4(0.3 – 0.6)*	CBC	1.2(0.8 – 1.7)
Geographical Location			
South-west	1.0	1.0	1.0
South-south	0.7(0.5 – 1.1)	1.4(1.1 – 1.7)*	0.9(0.7 – 1.3)
South-east	1.3(0.9 – 1.7)	1.0(0.9 – 1.3)	1.0(0.7 – 1.6)
North-central	0.7(0.6 – 0.8)*	3.3(2.1 – 4.9)*	2.6(1.8 – 3.5)*
Family History of Prostate Cancer			
Yes	1.0	1.0	1.0
No	0.8(0.7 – 0.9)*	1.5(1.2 – 2.0)*	1.1(0.7 – 1.4)
Method of diagnosis			
PSA test	1.0	1.0	1.0
NB: CBC = can't be computed; Overall = 2010 - 2017; CrI = Credible Interval			
* = statistically significant			

Characteristic	2010 – 2014	2015 - 2017	Overall
DRE test	0.9(0.9 – 1.0)	1.4(0.9 – 1.9)	1.4(1.0 – 1.9)*
Transrectal Ultrasound	0.5(0.4 – 0.7)*	0.9(0.6 – 1.4)	0.8(0.4 – 1.4)
Biopsy	0.7(0.6 – 0.8)*	0.9(0.7 – 1.2)	1.1(0.8 – 1.4)
DRE & Biopsy	0.6(0.5 – 0.8)*	2.1(1.5 – 2.7)*	1.4(0.9 – 1.9)
Gleason group			
Well differentiated	1.0	1.0	1.0
Moderately differentiated	1.4(1.3 – 1.6)*	0.6(0.4 – 0.8)*	0.9(0.6 – 1.3)
Poorly differentiated	1.7(1.3 – 2.2)*	0.8(0.6 – 0.9)*	1.1(0.6 – 1.7)
PSA level	0.9(0.9 – 1.0)	1.0(0.9 – 1.0)	1.1(0.9 – 1.0)
Stage at Diagnosis			
Stage I	1.0	1.0	1.0
Stage II	0.5(0.4 – 0.6)*	0.9(0.7 – 1.2)	1.2(0.4 – 2.5)
Stage III	0.4(0.3 – 0.4)*	0.5(0.3 – 0.8)*	0.3(0.2 – 0.5)*
Stage IV	0.5(0.4 – 0.7)*	1.2(1.0 – 1.4)*	0.9(0.6 – 1.2)
Unknown	0.5(0.4 – 0.6)*	0.9(0.6 – 1.4)	0.5(0.4 – 0.7)*
Site of Metastasis			
Lymph node	1.0	1.0	1.0
Rectum (bladder neck)	0.9(0.6 – 1.4)	1.1(0.8 – 1.4)	0.7(0.5 – 0.9)*
Bones	0.9(0.7 – 1.2)	1.5(1.1 – 2.1)*	0.9(0.7 – 1.1)
Spine	0.7(0.6 – 0.9)*	1.3(1.1 – 1.6)*	0.8(0.5 – 1.1)
Multiple Metastasis	1.1(0.9 – 1.3)	1.3(0.9 – 1.9)	0.9(0.6 – 1.2)
Treatment Modality			
Surgery	1.0	1.0	1.0
Radiotherapy	0.7(0.7 – 0.8)*	1.0(0.8 – 1.4)	0.9(0.6 – 1.3)
Chemotherapy	1.2(1.5 – 2.1)*	0.9(0.8 – 1.2)	1.1(0.7 – 1.7)
Radiotherapy & Surgery	3.2(2.3 – 4.4)*	1.4(0.9 – 2.0)	2.4(1.3 – 4.5)*
Chemotherapy & Radiotherapy	1.6(1.3 – 1.9)*	1.7(1.2 – 2.3)*	2.1(1.3 – 2.9)*
Chemotherapy & Surgery	3.3(2.6 – 4.4)*	1.2(0.9 – 1.6)	1.9(1.4 – 2.7)*
Chemotherapy & Surgery & Radiotherapy	0.5(0.4 – 0.8)*	CBC	10.4(4.7 – 16.7)*
-2LL	959.3	900.8	1281.2
DIC	394.7	456.0	908.7
NB: CBC = can't be computed; Overall = 2010 - 2017; CrI = Credible Interval			
* = statistically significant			

Characteristic	2010 – 2014	2015 - 2017	Overall
<i>BIC</i>	932.7	928.2	1311.8
<i>AR</i>	0.4	0.3	0.3
<i>Efficiency</i>	0.2	0.1	0.1
NB: CBC = can't be computed; Overall = 2010 - 2017; CrI = Credible Interval			
* = statistically significant			

Discussion

This study accessed the time-to-remission among people with prostate cancer and assessed the determinants of prostate cancer remission. We found that the incidence of CaP was highest among patients older than seventy-two years. This finding is corroborated by outcomes of an earlier study by Ifere et al. [33]. CaP is known to be a disease of the aged with very few incidences observed among those below forty years, and very recurring as men progress in age. Advanced age is associated with an aggressive form of this disease [34] and a predictor for delayed remission as shown in this study.

The highest median time-to-remission in this study was observed among the CaP patients from the north-central region of Nigeria. This could be attributable to race and geographical variation and the distance patients had to travel to receive treatment. This is consistent with the literature [2, 21, 22]. A further plausible explanation could be the lack of functional treatment facility, industrial action by health workers, thereby resulting in a patient presenting at a time where remission could be negatively affected. This opinion was also shared by Zhang et al. [35]. Most patients either drink alcohol and/or smoke tobacco, these are known determinants for lung cancer, but it is not yet known if it could be a deterrent to CaP remission [36].

The majority of the diagnosis was done via DRE, closely followed by a biopsy, this is because DRE can indicate whether a prostate biopsy is recommended for a patient, especially in more aggressive cases [37]. Being diagnosed with DRE shortened time-to-remission. This could be due to its ability to quickly detect the hardness of the prostate indicating the presence of CaP. DRE is known to be an independent marker for a better prognosis for CaP [38]. However, this was not consistent with our findings which showed that diagnosis via transrectal ultrasound, biopsy and a combination of DRE and biopsy were markers that decreased time-to-remission.

The absence of a parent or first-degree male relative with a known case of CaP did impact the likelihood of experiencing remission among the CaP patients. Given the genetics and hereditary factors that come to play from one generation to another, it further highlights that there is every likelihood of this disease not recurring in another generation and is in agreement with an earlier finding [39].

A well-differentiated Gleason group was associated with better prognosis however moderately and poorly differentiated Gleason group was associated with delay time-to-remission. It was also observed that a large proportion of patients presented with either a moderately or poorly differentiated Gleason score. This could be due to a lack of adequate awareness of the importance of frequent medical check-ups and early presentation [40, 41]. As reported by Akinremi et al., most patients presented at an advanced stage [19]. This has become a recurring theme among Nigerian CaP patients. This may be a case of negligence and lack of regular awareness on the part of policy-makers. While on the part of the patients, distance and cost of receiving care may be responsible. As shown in this study late presentation was also a contributing factor to long time-to-remission and patients in this category often experience recurrence [38]. This is consistent with findings in a Ghanaian study [42]. This shows that early presentation particularly at stage I could shorten a patient's time-to-remission.

Most patients presented with metastasis especially in the spine and others with multiple metastases [19, 43]. It has been observed that before diagnosis, patients usually go through a series of assumptive diagnoses. Such that before the detection of such cancer, it has metastasized beyond the prostate region. Much more effort is needed particularly by policymakers to ensure early diagnosis and frequent screening practices. Paramount to remission is the management of CaP as most patients still experience residual and possible recurrence given the spread of this disease to advance areas, especially in the case of multiple metastases.

An elevated Prostate Specific Antigen (PSA) level at diagnosis is usually associated with poor disease prognosis, although due to differences in technical performance and reference standards, PSA measurements from different labs are not necessarily comparable. However, approximately 98% of patients with metastatic CaP will have elevated PSA [44]. In this study, PSA level did not affect treatment outcome. Observed among patients in this facility was the inconsistency of PSA levels during treatment. This could be due to a lack of proper care and lack of finance for consistent treatment on the part of patients, as some patients may miss a certain number of treatments before continuing treatment. Treatment via a combination therapy of chemotherapy, surgery and radiotherapy shortened time-to-remission and showed a better prognosis [45]. This may not be unrelated to the unaffordability of treatments among most patients, meaning very few patients have access to treatments that are capable of effectively triggering remission. Patients who received radiotherapy alone also experienced remission. However only a few patients received this treatment regimen, this could be due to the unavailability of a radiotherapy machine, coupled with frequent breakdown and workers industrial action [46–48].

A limitation of this study lies in the secondary nature of the data extracted limited our choice of explanatory variables and the completeness of the data used. It would be necessary to access this data in a prospective longitudinal study. Although the tertiary hospital used in this study attracts patients from all over the country, the patients could have been more skewed to the Southwest, so our findings on geographical differences should be interpreted with caution. Notwithstanding, we have used a robust statistical estimation procedure that enhances the reliability of our estimates while also taking into consideration the violation of the assumption of proportionality.

Conclusion

Prostate cancer still ranks among the second causes of cancer death among men. However, this trend could be deterred through awareness and early presentation which could mitigate against metastasis and progression to advanced stages. This study showed geographical variation in time to remission as apparent in some European and North American studies. We, therefore, conclude that central to the experience of remission in prostate cancer treatment are the age of the patient, family history of the disease, clinical factors such as the method of diagnosis, stage at diagnosis, site of metastasis and treatment received. Efforts should therefore be intensified to encourage regular prostate examination among men 40 years and above as well as an emphasis on early presentation.

Abbreviations

CaP – Prostate Cancer

PSA – Prostate Specific Antigen

DRE – Digital Rectal Examination

Declarations

COMPETING INTERESTS

Authors declare no conflict of interest

FUNDING SOURCES

The authors received no funding for this study

ETHICAL APPROVAL

Ethical approval was obtained from UI/UCH Ethics Committee of the University of Ibadan; approval reference: UI/EC/18/0492. Informed consent was obtained from all subjects and/or their legal guardian(s). All methods were carried out in accordance with relevant guidelines and regulations.

AUTHORS' CONTRIBUTION

RA and AFF contributed to the conception, design, and drafting of the manuscript. RA performed the statistical analysis and interpretation of results. MA assisted in reviewing the proforma used for data collection as well as secured data release. RA and AFF reviewed the statistical analysis and revised the manuscript draft. All authors read and approve the final manuscript.

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AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are available from University College Hospital Ibadan but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available.

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Figures

Figure 1

Probability of survival among 2010 – 2014 and 2015 – 2017 cohorts

Figure 2

MCMC Convergence diagnostics for stage at diagnosis for 2010 - 2014 cohort

Figure 3

MCMC Convergence diagnostics for treatment regimen for 2015 - 2017 cohort