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PREDICTING SURVIVAL TIME OF VICTIMS OF BRAIN TUMOR WITH ASSOCIATED RISK FACTORS IN OSUN STATE, NIGERIA.

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ABSTRACT

This paper assessed the length of life of patients and prognostic factors associated with the survival of brain tumour victims in Osun State, Nigeria. Data used were taken from patients' medical records on gender, age, status (survived or dead), admission, and discharge dates of brain tumours victims in Uniosun Teaching Hospital Osogbo, Osun State, from 2003 to 2022. Kaplan-Meier curve showed that < 80% of the brain tumor victims have a survival time of 210 days, there is more death in female patients than the male and 50% of the females have a survival time of 210 days whereas the males have no event but are censored. 15 out of 20 patients admitted survived brain tumour ailment with a median estimate of 210 days on an average of 50%. In Categorical Variable Coding of the hazard ratio, p-values > $\alpha = 0.05$ and the effect of age on victims is insignificant but the chances of teenagers, youths, and adult dying compared to children are 88%, 91%, and 88% respectively while females with a brain tumour have 88% of dying compared to the males. Overal $< \alpha = 0.05$ son of the victim's model coefficients is significant and best for predicting (p-value (0.006) as well as the chi-square distribution.

Keywords: Time-to-event, Brain tumour, Censoring, Kaplan Meier, Survival

1. BACKGROUND OF THE STUDY

Cancer is one of the main causes of death worldwide and many treatments have been developed, such as chemotherapy, surgery, and radiation therapy. Tumour cells are abnormal cells that are classified into benign and malignant. The benign tumours do not invade the normal tissue, while the malignant tumor invades and can spread around the body (Cooper, 2000). Malignant tumours are cancerous tumours and they have a growth rate much faster than normal cells.

Brain tumors are serious health problems that can have a significant impact on the lives of patients and their families. In Osun State, Nigeria, the incidence of brain tumors is relatively low compared to developed countries, but the survival rate is also lower.

Brain tumours can be categorized as primary and secondary. Primary brain tumors originate in the brain itself and are less common than secondary brain tumours. Secondary brain tumours are metastatic tumours that originate in other parts of the body and have spread to the brain. Tumours in the brain can be benign or malignant. A brain tumour can occur at any age and certain risk factors like exposure to ionizing radiation and family history of brain tumours play an important role.

Surgery is the primary option for the treatment of a brain tumour. In this operation, the surgeon removes a part or all of the tumours from the brain. It may be combined with chemotherapy or radiation therapy to effectively destroy tumour cells. The surgery is conducted by a neurosurgeon along with a multidisciplinary team including neurologists, medical and other specialists like paediatrics oncologists, and radiation oncologists depending on the patient's condition and age.

Brain tumour surgery is a major operation and should be performed at a recognized medical facility that has the necessary infrastructure and surgical equipment. The hospitals in Nigeria lack appropriate technological support and do not have qualified doctors for complex procedures like brain tumour surgery. As the medical facilities in the country are not as advanced as many other countries and most patients prefer to travel abroad for their treatment. India ranks amongst the top medical tourism destinations of the world and a large number of Nigerian patients visit India on a

medical tourist visa for all kinds of health procedures like cancer treatment, cardiology problems, neurological disorders, kidney transplant, enlarged prostate, and many others. The brain surgery cost in India is lower than in many other countries with equally good services and excellent brain tumour surgery success rates. The overall cost of treatment in India is highly affordable even after including the expense of travel, accommodation, and other logistics.

Statement of the Problem

Brain tumors are a serious medical condition that can have a devastating impact on patients and their families. The survival time for brain tumor patients varies widely, depending on the type of tumor, the stage of the disease, and the patient's overall health. In Nigeria, the survival time for brain tumor patients is generally lower than in other parts of the world.

Justification of the Study

This study is justified by the need to better understand the factors that affect the survival time of brain tumor patients in Osun State, Nigeria. By identifying these factors, we can develop targeted interventions to improve the survival time of these patients.

Significance of the Study

This study would be significant for many reasons: (i) First, it would provide much-needed information about the factors that affect the survival time of brain tumor patients in Osun State, Nigeria. This information could be used to develop targeted interventions to improve the survival time of these patients. (ii) Second, this study would help to raise awareness of the issue of brain tumors in Nigeria. This could lead to increased funding for research into brain tumors and improved access to care for brain tumor patients. (iii) Third, this study would contribute to the body of knowledge about brain tumors. This knowledge could be used to improve the care of brain tumor patients around the world.

Aim: This paper assessed the length of life of patients and prognostic factors associated with the survival of brain tumours victims in Osun State, Nigeria.

The specific objectives of this paper are to

(a) estimate the survival time of victims with brain tumours.

(b) estimate mean and median time of survival.

(c) assess the association of and impact of covariates (risk factors) on event status and survival time estimate survival time of victims with brain tumours.

2. LITERATURE REVIEWS

Brain tumours (BT) refer to a mixed group of neoplasms originating from intracranial tissues. There are two basic types of brain tumours: primary and metastatic brain tumours. Primary brain tumours originate and remain in the brain. Metastatic brain tumours originate from other organs in the body and spread to the brain. Primary brain tumours could equally be termed benign or malignant, depending on their ability to invade surrounding tissue. In 2015, the world annual incidence of primary brain tumour was estimated at 3.7 and 2.6 per 100,000 men and women, respectively, with a higher rate in developed (5.1/100,000) than developing countries (3.0/100,000). In African countries, little research has been conducted on the incidence of brain tumours. Davies in 1965 estimated central nervous system (CNS) tumours to represent 1.1% of all cancers registered in Uganda. A higher incidence was reported in a hospital-based cancer registry from 2009 to 2010 in Nigeria, where brain cancer represented 3.9% of total cancers.

There are a few rare, inherited genetic syndromes that are associated with brain tumours, including Neurofibromatosis 1 (NF1 gene), Neurofibromatosis 2 (NF2 gene), Turcot syndrome (APC gene), Gorlin syndrome (PTCH gene), Tuberous Sclerosis (TSC1 TSC2 genes) and Li-Fraumeni syndrome (TP53 gene). Although 5-10% of persons with brain tumours have a family history of a brain tumour, the vast majority of CNS tumours appear not to be a part of inherited genetic syndromes (Wrensch,

1997). Several studies have identified genetic variants that may be associated with an increased risk of certain brain tumours including glioma and meningioma. One such study is Gliogene, a study that was started in 2004 to find a familial link in brain cancer. A study from 2017 shows that while there are some hereditary similarities in glioma tumours between family members, there is not a statistically significant difference between families having tumours with similar hereditary features as compared to families with tumours having different hereditary features. Also, in families with more than one glioma, the tumours tend to have the same molecular markers.

In Africa, Davies's (1965) study was conducted in Uganda and found that the incidence of brain tumours was 1.1% of all cancers diagnosed in the country. The most common type of brain tumour was a meningioma, followed by a glioma and pituitary tumour. The average survival time for patients with brain tumours was 10 months. Eyenga *et al*. (2016) study was conducted in Douala, Cameroon, and found that the incidence of brain tumours was 2.6% of all cancers diagnosed in the city. The most common type of brain tumour was a meningioma, followed by a glioma and pituitary tumour. The average survival time for patients with brain tumours was 12 months.

In Nigeria, Soyemi and Oyewole's (2015) study was conducted in Nigeria and found that the incidence of brain tumours was 3.9% of all cancers diagnosed in the country. The most common type of brain tumour was a glioma, followed by meningioma and pituitary tumour. The average survival time for patients with brain tumours was 12 months. Soyemi and Oyewole (2015) observed that the peak age group for intracranial tumours in adults was 25–30 years. Owolabi *et al.* (2022) conducted research on brain cancer in Nigeria and found that the incidence of brain tumours was 4.1% of all cancers diagnosed in the country. The most common type of brain tumour was a glioma, followed by meningioma and pituitary tumour. The average survival time for patients with brain tumours was 12 months. Also, Adekunle *et al*. (2023) observed in their study conducted that the most common risk factors for brain tumours in Nigeria were exposure to ionizing radiation, family history of brain tumours, and genetic mutations. The study also found that the incidence of brain tumours in Nigeria is increasing and that this increase is likely due to a combination of factors, including environmental pollution, diet, and lifestyle. Idowu *et al*. (2023) found that the average age of diagnosis for brain tumours in the country is 45 years old. The study also found that the most common symptoms of brain tumours in Nigeria are headache, nausea and vomiting, seizures, and vision problems.

3. METHODOLOGY

The data used were taken from patients' medical records on gender, age, and status of victims (survived or dead), admission, and discharge dates of brain tumours victims in Uniosun Teaching Hospital Osogbo, Osun State, from 2003 to 2022.

Time-to-event models, commonly known as survival or reliability model, have been studied and applied in a variety of scientific disciplines such as medicine, biology, engineering, and business. Cox proportional hazards model is one of the most commonly used nonparametric/semi-parametric models; it does not require any specific assumption about the shape of the survival function. However, it usually does not provide a very good fit for the data through the simulation studies. On the other hand, if the assumption for parametric distribution is met for the data under consideration, it will be more efficient and easier to interpret estimates than nonparametric/semi-parametric models. Some well-established parametric models, such as Weibull, log-normal and log-logistic models have been widely used to model the time to event data in many applications.

Kaplan-Meier curve

Kaplan-Meier curve was used to estimate the survival time of the brain tumor victims. Itestimates the survival chance at a specific time, which is given in the following models and associated standard error in model **:

$$S(t_{j+1}) = \prod_{j=1}^{k}\left(1 - {}^{d_j}/_{n_j}\right) \quad (1)$$

$$S(t)\sqrt{\sum_{j=1}^{k}\frac{d_j}{n_j(n_j-d_j)}} \quad (2)$$

To compare the significance of two survival curves we use the $\boldsymbol{Tarone-Ware}$ approach as follows:

$$(T) = \frac{U^2}{V} \sim \chi^2(1) \quad (3)$$

$$U = \sum_{j=1}^{m}\sqrt{n_j}(d_j^A - e_j^A) \quad (4)$$

$$\boldsymbol{while} V = var(U) = \sum_{j=1}^{M}\frac{n_j^A n_j^B d_j(n_j-d_j)}{n_j(n_j-1)} \quad (5)$$

Variables considered in survival analysis are:

(a) Serial time: This is the duration of known survival which is terminated by the event of interest. This is graphed as a horizontal line

(b) Status at the end of their serial time: This is the event of interest which can either be death or alive

(c) The study group they are in: These are groups to which the subjects under study belong. to

Why censoring in survival analysis?

(a) This happens when something negative happens such as: (a) Subject under study drops out. (b) The subject is lost to follow-up. (c) Required data are unavailable

(b) This happens when something good happens such as the study ends before the subject had the event of interest occur i.e., they survived at least until the end of the study, but there is no knowledge of what happened thereafter. Censoring occurs within the study or terminally at the end.

The lengths of horizontal lines along the x-axis of Kaplan Meier survival curves of serial times represent the survival duration for that interval. The interval is terminated by the occurrence of the event of interest while the vertical lines are just for cosmesis; they make the curve more pleasing to observe. The vertical distances between horizontals illustrate the change in cumulative time probability as the curve advances. The non-continuous nature of the curve emphasizes that they are not smooth functions but rather step-wise estimates; thus, calculating a point survival can be difficult. The steepness of the curve is determined by the survival duration (length of horizontal lines).

Cox Regression (or proportional hazards regression): The coefficients in a Cox regression relate to hazard; a positive coefficient indicates a worse prognosis and a negative coefficient indicates a protective effect of the variable with which it is associated.

4. DISCUSSION OF RESULTS

KAPLAN-MEIER ANALYSIS

Total N	N of Events	Censored N	Percent
20	5	15	75.0%

Table 2: Means and Medians for Survival Time

Mean[a]				Median			
		95% Confidence Interval				95% Confidence Interval	
Estimate	Std. Error	Lower Bound	Upper Bound	Estimate	Std. Error	Lower Bound	Upper Bound
334.495	35.795	264.336	404.653	416.000	131.282	158.687	673.313

a. Estimation is limited to the largest survival time if it is censored.

Fig 1: KAPLAN-MEIER CURVE OF BRAIN TUMOUR VICTIMS

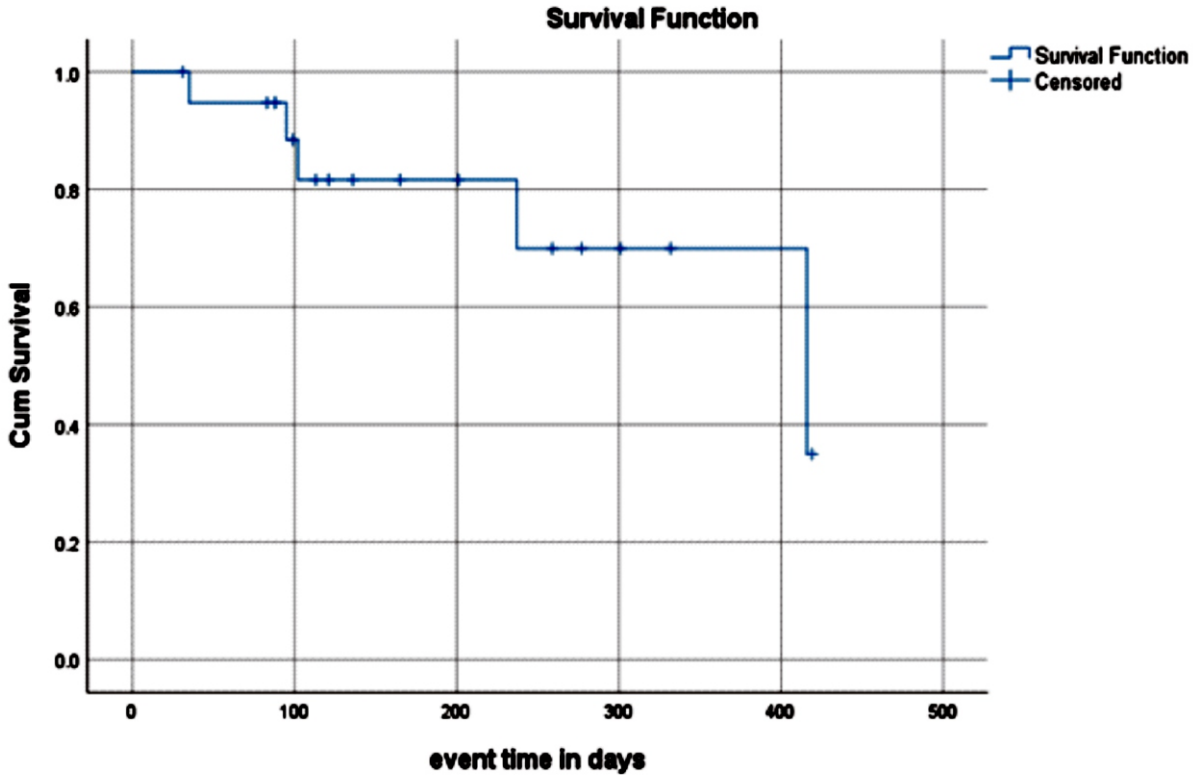


Fig 1: KAPLAN-MEIER CURVE OF BRAIN TUMOUR VICTIMS

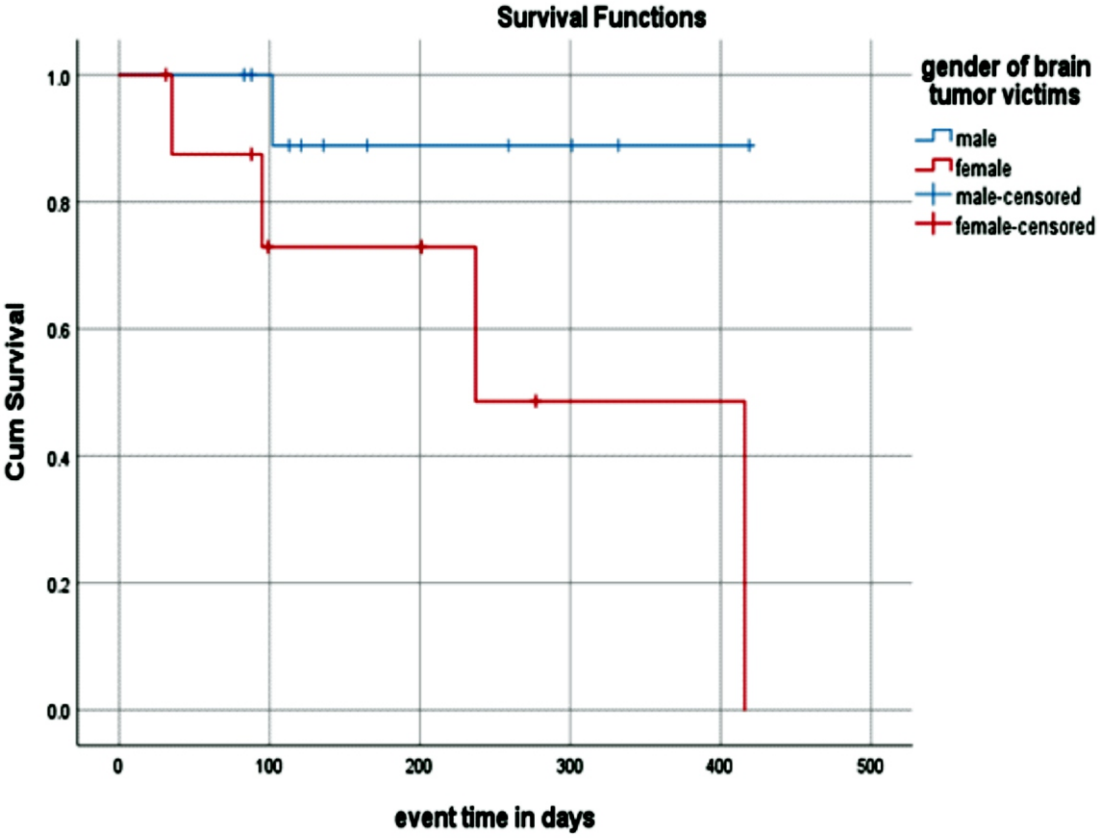


Fig 2: KAPLAN-MEIER CURVE OVER GENDER CATEGORIES

COX REGRESSION

Table 3: Categorical Variable Codings[a,c]

		Frequency	(1)	(2)	(3)
gender of brain tumour victims	1=male	11	0		
	2=female	9	1		
age of brain tumour victims	1.00=<=12 years (children)	6	0	0	0
	2.00=13-19 (teenagers)	4	1	0	0
	3.00=20-40 (youth)	4	0	1	0
	4.00=>40 adults	6	0	0	1

a. Category variable: gender of brain tumour victims (sex)
b. Indicator Parameter Coding
c. Category variable: age of brain tumour victims (age)

Table 4: Variables in the Equation

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B) Lower	Upper
gender of brain tumour victims	18.608	121.710	.023	1	.878	120632025.986	.000	4.798E+111
age of brain tumour victims			.787	3	.853			
age of brain tumour victims (1)	26.976	185.234	.021	1	.884	519616620519.000	.000	2.441E+169
age of brain tumour victims (2)	9.582	80.638	.014	1	.905	14497.221	.000	6.311E+72
age of brain tumour victims (3)	28.111	185.235	.023	1	.879	1615551251921.508	.000	7.592E+169

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Table 6: **Data on admission date, discharge date, gender, age, and status of patients with cervical cancer in Uniosun Teaching Hospital Osogbo, Osun State.**

Admission date	Discharged date	Gender	Age	Status
19.02.2003	14.10.2003	Female	24.00	Death
02.05.2007	31.08.2007	Male	2.00	Alive
09.10.2008	25.06.2009	Male	13.00	Alive
11.03.2009	23.08.2009	male	35.00	Alive
05.12.2009	03.03.2010	female	6.00	Alive
20.01.2012	20.02.2012	female	50.00	Alive
12.03.2011	01.05.2012	female	7.00	Death
04.04.2011	27.05.2012	male	37.00	Alive
19.02.2012	16.01.2013	male	4.00	Alive
05.09.2012	09.06.2013	female	2.00	Alive
12.08.2012	09.06.2013	male	4.00	Alive
03.02.2014	09.05.2014	female	53.00	Death
14.04.2014	19.05.2014	female	17.00	Death
18.03.2014	09.06.2014	male	37.00	Alive
04.03.2021	18.07.2021	male	52.00	Alive
18.10.2021	14.01.2022	male	71.00	Alive
12.11.2021	22.02.2022	male	71.00	Death
09.12.2021	18.03.2022	female	15.00	Alive
21.01.2022	14.05.2022	male	71.00	Alive
05.02.2022	25.08.2022	female	5.00	Alive

4.1 SUMMARY OF RESULTS

The dependent variable in this study is the survival time data (T) of victims with a brain tumour. Survival time (T) is when patients who have brain tumour undergo treatment at Uniosun Teaching Hospital Osogbo until the patient is declared dead, stopped or moved on treatment, survives, or lives in units of the day.

The provisions of the survival time (T) are as follows.

(a) The time origin is when the initial patient enters the hospital for hospitalization due to a brain tumour.

(b) Failure (failure event) is a condition when a victim with a brain tumor is declared dead.

(c) The measurement scale of this study is in units of days. Patient status (D) is the occurrence or failure of a failure event that is dead during the study period.

(d) Patient status d = 1, is censored data. It happens if the patient has not experienced a failure event until the study ends, stops, or changes treatment. Patient status (d) is the occurrence or failure of a failure event that is dead during the study period.

(e) Patient status d = 2, is event or uncensored data. It happens if a brain tumor patient experiences a failure event, which is death.

Interpretation of Tables and Graphs

Table 1 above describes the available data collected for this research which includes: the age of patients, gender of patients, admission date of patients, discharge date of patients, and the status of events i.e., survive (15) and non-survive (5) of twenty patients who were victims of a brain tumour at Uniosun Teaching Hospital Osogbo, Osun State.

Table 2 shows the means and medians for Survival Time of the brain tumour victims under study with an estimate of 416 days when using the median estimate. Averagely, 50% of the brain tumour's victims survive in 416 days.

The Kaplan-Meier curve of brain tumour victim's Fig 1, revealed the distribution of the data as censored with the (+) sign on the stair of the graph while the vertical lines showcased the event (death) that occurred. Less than 80% of the victim has a survival time of 210 days. On the other hand, fig 2 Kaplan-Meier curve over gender categories shows there are more deaths in female patients compared to that of male where 50% of the female has a survival time of 210 days whereas the males have no event (death) but are censored.

Table 3 revealed Categorical Variable Coding which assesses the relationship between survival times of the risk factors (gender and age group) where a female is considered about the male and other age groups are considered about age group less than 12 years. The Exp(B) column shows the hazard ratio, the age has no significant effect same as gender on the survival time of the brain tumour victims since the sig values i.e., the p-values are greater than the alpha level of 0.05 or when the lower and upper limits contain 1. Although, the effect of age on victims is non-significant the chances of teenagers, youths, and adult dying compared to children are 88%, 91%, and 88% respectively. The females with a brain tumour have 88% dying compared to the males.

Table 5 showedthe overall comparison of the victim's model coefficients is statistically significant and best for predicting since the p-value (0.006) is less than the alpha level = 0.05 same as the chi-square distribution.

5. CONCLUSION

Survival analysis has essential importance for brain tumours to assess the length of life of patients and prognostic factors associated with the survival of brain tumours victims in Uniosun Teaching Hospital Osogbo, Osun State. However, the following conclusions are drawn based on the results provided above:

(a) The study found that the median survival time for brain tumor victims was 416 days. This means that 50% of the victims survived for at least 416 days. The Kaplan-Meier curve showed that less than 80% of the victims survived for 210 days.

(b) The study also found that gender and age group were not significant predictors of survival time. However, the chances of death were higher for teenagers, youths, and adults compared to children. The females with brain tumors also had a higher chance of death than the males.

(c) The overall model was statistically significant and best for predicting survival time. This means that the factors included in the model were able to explain a significant

6. RECOMMENDATIONS

The following recommendations based on this study should be looked into:

1. Workshops /awareness on early diagnosis of patients with tumours relating to the brain should be made available for the populace by the government through seminars and regular check-ups.
2. Treatments given to victims of brain tumour patients in Uniosun Teaching Hospital Osogbo should be improved or new interventions should be sourced to increase the survival time of patients with brain tumours visiting the hospital.

3. Government should assist in arming hospitals with advanced interventions and diagnostic tools which would be used in treating brain tumor victims.
4. Some of the patient's medical records did not have all the required risk factors needed for this study; hence we are limited by only the information at our disposal. Development of this study with more risk factors is advised.

7. FURTHER STUDY

Further research is needed to identify other factors that may affect the survival time of brain tumour victims.

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