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SURVIVAL ANALYSIS OF PATIENTS WITH CHRONIC HEPATITIS B AT THE FEDERAL MEDICAL CENTRE, NGURU

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Article Info

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Abstract

Background: Hepatitis B Virus (HBV) infection remains a major cause of liver-related morbidity and mortality, particularly in sub-Saharan Africa (SSA). Despite the high prevalence of HBV in Nigeria, few studies have assessed the survival patterns of affected patients in the northern region.

Methods: This retrospective cohort study included 150 patients with confirmed chronic hepatitis B who received care at the Federal Medical Centre, Nguru, between January 2019 and December 2024. Survival time was calculated from diagnosis to death or censoring. Kaplan–Meier survival estimates and log-rank tests were used for univariate analysis. The effects of age, sex, liver biopsy results, AST and ALT enzyme levels, antiviral therapy, viral load, and comorbidities on patient survival were assessed using the Cox proportional hazards model.

Results: The model diagnostics confirmed that the proportional hazards assumption was not violated ($p = 0.2278$), and the model demonstrated strong predictive power with a Harrell's C-statistic of 0.845. Age (HR ≈ 1.03, $p = 0.043$), advanced liver fibrosis or cirrhosis (HR ≈ 3.15, $p = 0.024$), and comorbid conditions such as HIV, diabetes, or hypertension (HR ≈ 4.11, $p = 0.003$) were associated with significantly increased hazard of death. Antiviral therapy, particularly tenofovir, was found to reduce the hazard by approximately 77% (HR ≈ 0.23, $p < 0.001$), demonstrating a strong protective effect. Gender and elevated AST levels showed weak but positive associations with increased hazard, though not strongly significant at the 5% level. The

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median survival time was 44 months (95% confidence interval [CI]: 41–53). Kaplan–Meier analysis demonstrated significantly poorer survival in patients with comorbidities and advanced liver disease.

Conclusion: Age, liver fibrosis, comorbidities, and antiviral therapy were the major determinants of survival among patients with chronic hepatitis B at the Federal Medical Centre, Nguru. This study highlights the importance of early diagnosis, routine fibrosis assessment, and timely initiation of antiviral therapy in improving the survival of patients with chronic hepatitis B in resource-constrained settings. The findings of this study provide valuable evidence for clinicians and policymakers aiming to improve hepatitis B management and reduce liver-related deaths in Northern Nigeria.

1.0 Introduction

Hepatitis B Virus (HBV) infection is a major global public health problem, with over 296 million people estimated to be living with chronic HBV infection as of 2019 (World Health Organization, 2021). It is a leading cause of chronic liver disease, including cirrhosis and Hepatocellular Carcinoma (HCC), contributing significantly to global morbidity and mortality (Schweitzer et al., 2015). The burden of HBV remains endemic in sub-Saharan Africa, including Nigeria (Musa et al., 2015). Chronic Hepatitis B (CHB) is a long-term infection that persists in the liver, leading to progressive liver damage over decades. The natural history of CHB is influenced by various factors, including viral load, age of acquisition, host immune response, and co-infections (Kim et al., 2016). While some individuals remain asymptomatic carriers, others develop severe complications, such as cirrhosis and liver failure, reducing their survival rates (Liaw & Chu, 2009). In Africa, Nigeria is ranked as a country with hyper-endemic HBV infection (>8%). Approximately nine in ten Nigerians who live with chronic HBV are unaware of their infection status and are missing from the global public health statistics due to a lack of resources, awareness, and political will for addressing Nigeria's HBV plight. Consequently, Nigeria has one of the highest rates of HBV-attributable cancer in West Africa, with an estimated age-standardized incidence of 2.6 to <5.1 cases per 100,000 person years. The prevalence of HBV varies by region in Nigeria, with Northern Nigeria showing a great burden of the disease (Musa et al., 2015). The Federal Medical Centre (FMC) Nguru, located in Yobe State, serves as a referral center for managing infectious diseases, including HBV. Despite the available treatment options, such as tenofovir and entecavir, many patients present with late advanced liver disease, affecting their survival outcomes (Olayinka et al., 2016). Understanding the survival outcomes of patients with chronic hepatitis B in FMC Nguru is crucial for guiding clinical decision-making, improving treatment strategies, and informing public health interventions aimed at reducing HBV-related mortality in the region.

2.0 Methods

Research Design

A retrospective cohort study design was used to analyze the survival of patients with chronic hepatitis B. The study used the Cox proportional hazards model to track patients over time to determine survival rates and identify significant risk factors affecting their survival and assess the impact of covariates on patient survival.

Source and Collection of Data

This study will use data obtained from the medical records of patients with chronic hepatitis B managed at the Federal Medical Centre, Nguru. The study covered a 6-year period from January 2019 to December 2024 to ensure adequate number of survival events and sufficient follow-up duration for meaningful analysis. Secondary

data were collected using a structured data extraction form, designed to systematically retrieve relevant demographic, clinical, and survival-related information from patient case files. The records include patient demographics, clinical characteristics, treatment regimens, and follow-up survival status. Only patient records that met the predefined inclusion criteria were included, such as confirmed diagnosis of chronic hepatitis B, initiation of treatment within the study period, and availability of follow-up data. A convenience sampling technique was adopted to select 150 eligible patients. Each patient was followed from the date of diagnosis or initiation of treatment until the occurrence of the event (death), loss to follow-up, or the end of the study period (December 31, 2024), whichever came first. A minimum follow-up duration of 2 years was ensured.

Model Specification

The Cox proportional hazards model was used to assess the relationship between patient characteristics and survival. The hazard function is given as follows:

$$h(t|x) = h_0(t)\exp(\beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \cdots + \beta_8 x_8) \quad (2.1)$$

Where:

$h(t|x)$ Is the hazard function at time t, given covariates x

$h_0(t)$ Is the baseline hazard function.

$\beta_1, \beta_2, \ldots, \beta_8$ Are regression coefficients representing the impact of each independent variable on survival.

Variables and their Descriptions

The survival analysis includes both dependent and independent variables as follows:

Dependent Variable:

t = Survival time (in months or years) from diagnosis or treatment initiation until death or censoring (alive).

δ = Censoring indicator (1 if the patient died, 0 if censored or alive).

Independent (Covariate) Variables:

The independent variables included in the Cox model are as follows:

x_1=Age at diagnosis (years)

x_2=Gender (1 = male, 2 = female)

x_3=ALT levels (alanine aminotransferase, IU/L)

x_4=AST levels (Aspartate Aminotransferase, IU/L)

x_5=HBV DNA viral load (copies/mL)

x_6=METAVIR Fibrosis Stage (1 = advanced fibrosis, 2 = cirrhosis)

x_7=Comorbidities (1 = Yes, 0 = No)

x_8=Antiviral treatment received (1 = tenofovir, 2 = entecavir)

Hence:

$$h(t|x) = h_0(t)\exp(\beta_1 \text{Age} + \beta_2 \text{Gender} + \beta_3 \text{ALT} + \beta_4 \text{AST} + \beta_5 \text{ViralLoad} + \beta_6 \text{METAVIR} + \beta_7 \text{Comorbidities} + \beta_8 \text{Antiviral}) \quad (2.2)$$

Kaplan–Meier Survival Curve

In this study, the Kaplan-Meier survival curve was employed to visualize and compare the survival experiences of patients with chronic hepatitis B across different subgroups, such as sex, age categories, biopsy findings, and biochemical markers (e.g., AST and ALT levels). The curve plots the estimated survival probability on the y-axis against time (in months) on the x-axis. Each drop in the curve represents an event (e.g., death), whereas flat portions indicate intervals where no events occurred. The log-rank test will be used to assess the statistical significance of differences in survival curves among groups. This test evaluates whether the observed differences between survival curves are likely due to chance or reflect a true difference in survival distributions.

Model Assumptions

The Cox model assumes:

i. The HRs remain constant over time.
ii. The effect of covariates on the log-hazard is linear.
iii. The probability of censoring is independent of the survival time.

Evaluation and Validation of the Model

This assesses how well the model fits the data and its predictive performance.

Goodness-Of-Fit Tests

Goodness-of-fit tests assess how well a Cox model captures the data's underlying hazard structure. They help determine if the chosen model specification is adequate or if modifications (e.g., inclusion/exclusion of covariates, transformation of variables) are needed.

The Schoenfeld residuals test

Schoenfeld residuals are used to assess the proportional hazards assumption, a key assumption in Cox models that assumes that the HRs remain constant over time. The Schoenfeld residual is the difference between the observed covariate value for the subject experiencing the event and the weighted average of the covariate values for subjects at risk at each event time and each covariate in the model.

Cox- Snell Residuals

For a Cox model, the Cox-Snell residual for *the i*-th participant is defined as the cumulative hazard evaluated at the observed survival time using the fitted model. If the model fits well, the residuals should follow an exponential distribution with a hazard rate of 1. Plotting the Cox-Snell residuals' cumulative hazard function against a 45-degree line.

Likelihood Ratio Test

The likelihood ratio (LR) test is a fundamental statistical procedure used to compare the fit of two nested models, a full model versus a reduced model, by comparing their likelihoods.

Log-Likelihood:

For the Cox model, the partial likelihood is maximized to estimate the regression coefficients. The log-partial likelihood of the full model as ℓ_F and that of the reduced model (with fewer covariates or constraints) as ℓ_R.

Test Statistic:

The LR test statistic is calculated as follows:

$$\Lambda = -2(\ell_F - \ell_R) \quad (2.3)$$

Under the null hypothesis (i.e., the reduced model is true), Λ approximately follows a chi-squared distribution with degrees of freedom equal to the difference between the two models' estimated number of parameters.

Model Comparison:

The LR test is used to determine whether additional covariates significantly improve the model. For example, if testing whether a new predictor adds information, compare the model with and without the predictor.

Concordance Index (C-index)

The Concordance Index C-index is a measure of the predictive accuracy of a survival model. It assesses how well the model predicts the survival time order.

The C-index evaluates the proportion of all usable patient pairs (i.e., pairs in which the patient experienced the event first) where the predictions and outcomes are concordant.

For each pair of subjects, if the subject with a higher predicted risk (or lower survival probability) experiences the event before the other, the pair is considered "concordant." The C-index is computed as follows:

$$\text{C-index} = \frac{\text{Number of Concordant Pairs}}{\text{Number of Comparable Pairs}} \quad (2.4)$$

3.0 Results

Application to Chronic Hepatitis B Data

Table 3.1: Summary statistics of categorical data for CHB

Covariates	Categories	Status		Total
		Censored (%)	Event (%)	
Gender	Male	59(59.0)	41(41.0)	100
	Female	32(64.0)	18(36.0)	50
Marital Status	Single	44(88.0)	6(12.0)	50
	Married	44(45.36)	53(54.64)	97
	Divorced	3(100.0)	0(0.0)	3
Occupation	Student	43(87.76)	6(12.24)	49
	Farmer	14(34.15)	27(65.85)	41
	Civil Servant	17(70.83)	7(29.17)	24
	Housewife	14(48.28)	15(51.72)	29
	Teacher	0(0.0)	1(100.0)	1
	Fisherman	2(66.67)	1(33.33)	3
	Businessman	1(33.33)	2(66.67)	3
METAVIR fibrosis stage	Advanced Fibrosis	91(64.08)	51(35.92)	142
	Cirrhosis	0(0.0)	8(100.0)	8
Antiviral	Tenofovir	2(4.65)	41(95.35)	43
	Entecavir	89(83.18)	18(16.82)	107
Comorbidities	Yes	78(92.86)	6(7.14)	84
	No	13(19.70)	53(80.30)	66

Source: Computed using STATA

Table 3.2: Summary statistics of quantitative data for CHB

Covariates	N	Minimum	Maximum	Sum	Mean	Std. Deviation
Age at diagnosis	150	17	81	5836	38.91	15.384
Baseline AST (U/L)	150	137	365	35565	237.10	44.186
Baseline ALT level (U/L)	150	134	375	36378	242.52	45.458
Baseline viral load (IU/mL)	150	13107	41897	3740375	24935.83	4810.236

Source: Computed using STATA

Cox proportional hazard model results

Table 3.3: Cox proportional hazard model for chronic hepatitis B data

Covariates	B	HR	S. E	P-value
Gender	.601	1.824	.353	0.089
Age at diagnosis	.025	1.025	.012	0.043**
METAVIR fibrosis stage	1.146	3.145	.507	0.024**
Baseline AST (U/L)	.014	1.014	.008	0.097
Baseline ALT level (U/L)	.011	1.989	.008	0.159
Baseline viral load	.000	1.000	.000	0.359
Comorbidities	1.414	4.114	.475	0.003***
Antiviral	-1.47	0.229	.364	0.000***
		Likelihood ratio (θ): $\chi^2 = 76.29$; prob. =0.000***		

Source: Computed using SPSS

Kaplan–Meier Survival Curve Analysis for Data on Chronic Hepatitis B

Table 3.4: Survival Table for Chronic Hepatitis B

Interval (Months)	Beg. Total	Deaths	Lost	Survival Rate	Std. Error	[95% Conf. Int.]
17 18	150	2	0	0.9867	0.0094	0.9477 0.9966
19 20	148	1	0	0.9800	0.0114	0.9393 0.9935
20 21	147	2	0	0.9667	0.0147	0.9218 0.9860
21 22	145	0	1	0.9667	0.0147	0.9218 0.9860
22 23	144	0	3	0.9667	0.0147	0.9218 0.9860
23 24	141	0	1	0.9667	0.0147	0.9218 0.9860
24 25	140	7	6	0.9173	0.0229	0.8589 0.9522
25 26	127	3	2	0.8954	0.0256	0.8324 0.9356
26 27	122	2	8	0.8803	0.0273	0.8143 0.9239

27	28	112	3	2	0.8565	0.0298	0.7861 0.9051
28	29	107	3	8	0.8315	0.0322	0.7569 0.8850
29	30	96	2	5	0.8137	0.0339	0.7361 0.8705
30	31	89	2	2	0.7952	0.0356	0.7147 0.8554
31	32	85	0	1	0.7952	0.0356	0.7147 0.8554
32	33	84	1	5	0.7855	0.0365	0.7033 0.8473
33	34	78	0	1	0.7855	0.0365	0.7033 0.8473
35	36	77	1	2	0.7751	0.0374	0.6912 0.8389
36	37	74	0	2	0.7751	0.0374	0.6912 0.8389
37	38	72	3	7	0.7412	0.0406	0.6514 0.8112
38	39	62	3	5	0.7038	0.0439	0.6081 0.7804
39	40	54	3	3	0.6636	0.0471	0.5622 0.7468
40	41	48	3	4	0.6203	0.0503	0.5138 0.7100
41	42	41	2	5	0.5881	0.0526	0.4779 0.6827
42	43	34	2	0	0.5535	0.0549	0.4398 0.6532
43	44	32	2	5	0.5160	0.0572	0.3990 0.6210
44	45	25	2	2	0.4730	0.0600	0.3523 0.5844
45	46	21	1	0	0.4505	0.0612	0.3284 0.5649
48	49	20	1	2	0.4268	0.0624	0.3035 0.5443
49	50	17	0	2	0.4268	0.0624	0.3035 0.5443
50	51	15	1	0	0.3983	0.0644	0.2729 0.5208

51	52	14	0	1	0.3983	0.0644	0.2729 0.5208
52	53	13	1	2	0.3651	0.0670	0.2369 0.4942
53	54	10	1	0	0.3286	0.0696	0.1987 0.4646
54	55	9	0	1	0.3286	0.0696	0.1987 0.4646
56	57	8	0	1	0.3286	0.0696	0.1987 0.4646
57	58	7	2	0	0.2347	0.0750	0.1073 0.3902
58	59	5	0	1	0.2347	0.0750	0.1073 0.3902
62	63	4	1	0	0.1760	0.0758	0.0594 0.3434
63	64	3	0	1	0.1760	0.0758	0.0594 0.3434
65	66	2	1	0	0.0880	0.0729	0.0088 0.2875
66	67	1	1	0	0.0000	.	. .

Source: Computed using STATA

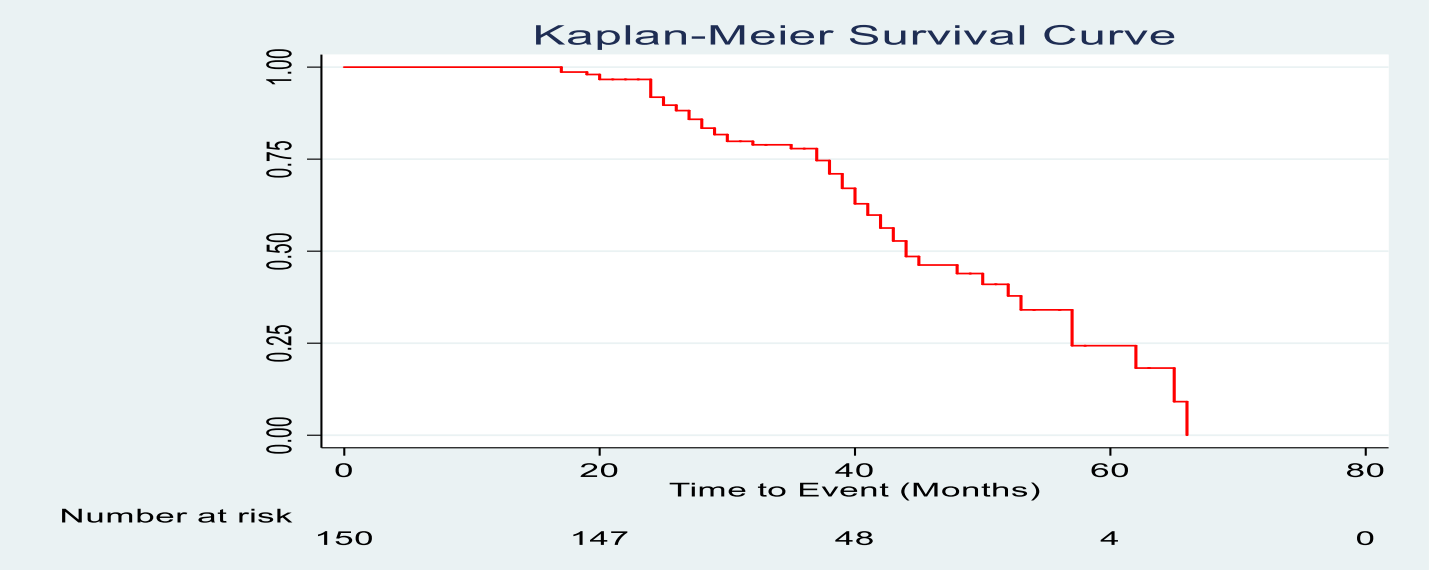

FIGURE 3.1: ***The Kaplan–Meier survival curve for the Cox model***

The Kaplan–Meier survival estimate in Fig. 3.1 shows a gradual but steady decline in the survival probability of patients with chronic hepatitis B over time, particularly from 20 to 60 months. Survival drops from nearly 100% to 0%, with the steepest decline occurring between 30 and 60 months. The small number of patients at risk toward the end of the follow-up period reflects that most patients either experienced the event or were censored. This curve shows that long-term survival among these patients is limited, and early intervention, especially within the first 2-3 years, may be critical.

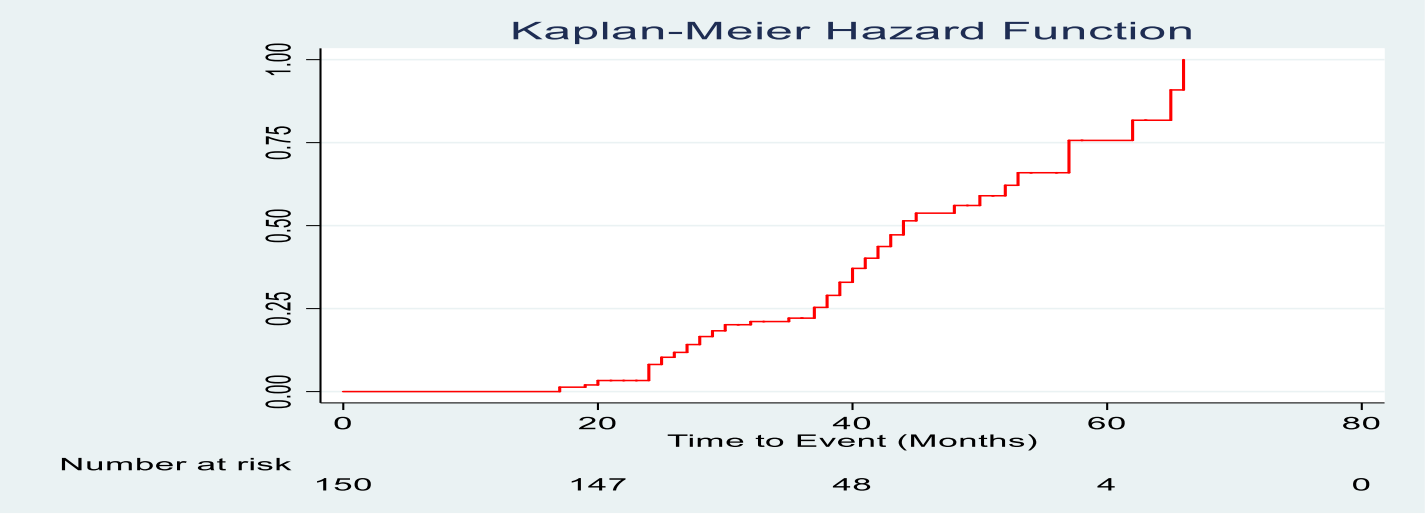

FIGURE 3.2: ***The Kaplan–Meier hazard curve for the Cox model***

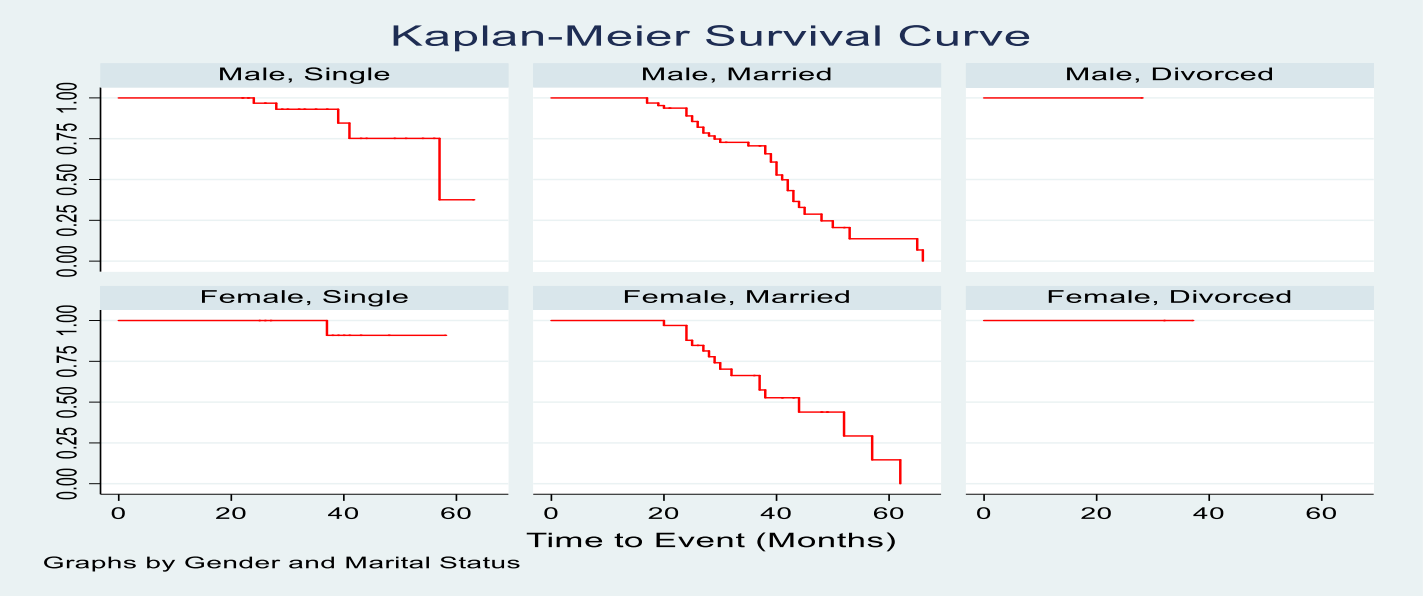

FIGURE 3.3: ***The Kaplan–Meier survival curve for subgroups***

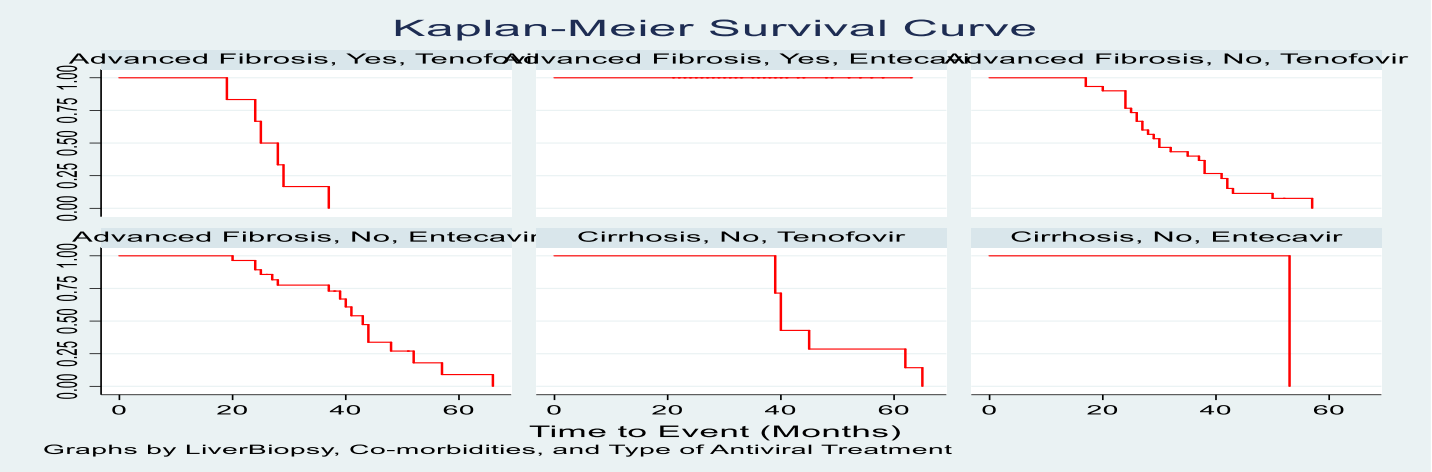

FIGURE 3.4: ***The Kaplan–Meier survival curve for subgroups***

Analysis of the median survival times

Table 3.5: Median survival times by subgroup

Sex	**Liver Biopsy**	**Antiviral**	**Comorbidities**	**Number of subjects**	**50% Median survival (months)**	**Std. Err.**	**95% confidence interval**
Male	Advanced	Tenofovir	Yes	3	24	4.08	19 –.
Male	Advanced	Tenofovir	No	24	28	4.41	25–41
Male	Advanced	Entecavir	Yes	50	.	.	. – .
Male	Advanced	Entecavir	No	16	43	2.12	39 –.
Male	Cirrhosis	Tenofovir	No	6	40	0.58	39 –.
Male	Cirrhosis	Entecavir	No	1	.	.	. – .
Female	Advanced	Tenofovir	Yes	3	28	2.45	25 –.
Female	Advanced	Tenofovir	No	6	30	1.84	24 –.
Female	Advanced	Entecavir	Yes	28	.	.	. – .
Female	Advanced	Entecavir	No	12	44	10.66	24 –.
Female	Cirrhosis	Tenofovir	No	1	.	.	. – .
Total				**150**	**44**	**2.87**	**41–53**

Source: Computed using STATA

Log-Rank Test

Table 3.6: Log-Rank Test for Survivor Function Equality

Sex	Marital Status	Liver Biopsy	Comorbidity	Antiviral	Events Observed	Events Expected
Male	Single	Advanced Fibrosis	Yes	Entecavir	0	9.55
Male	Single	Advanced Fibrosis	No	Tenofovir	3	1.59
Male	Single	Advanced Fibrosis	No	Entecavir	2	2.05
Male	Married	Advanced Fibrosis	Yes	Tenofovir	3	0.30
Male	Married	Advanced Fibrosis	Yes	Entecavir	0	6.63
Male	Married	Advanced Fibrosis	No	Tenofovir	19	6.43
Male	Married	Advanced Fibrosis	No	Entecavir	7	7.00
Male	Married	Cirrhosis	No	Tenofovir	6	4.53
Male	Married	Cirrhosis	No	Entecavir	1	1.05
Male	Divorced	Advanced Fibrosis	No	Tenofovir	0	0.18
Female	Single	Advanced Fibrosis	Yes	Entecavir	0	6.12

Female	Single	Advanced Fibrosis	No	Tenofovir	1	0.29
Female	Single	Advanced Fibrosis	No	Entecavir	0	0.12
Female	Married	Advanced Fibrosis	Yes	Tenofovir	3	0.57
Female	Married	Advanced Fibrosis	Yes	Entecavir	0	4.88
Female	Married	Advanced Fibrosis	No	Tenofovir	5	1.08
Female	Married	Advanced Fibrosis	No	Entecavir	8	4.42
Female	Married	Cirrhosis	No	Tenofovir	1	1.58
Female	Divorced	Advanced Fibrosis	Yes	Entecavir	0	0.52

Source: Computed using STATA

Total number of events observed: 59

The total events expected: 59.00

Chi-squared (df = 18) = 111.52

P = 0.0000

Model diagnostics and assumptions

Proportionality Assumption Test

Table 3.7: Proportional Hazard Assumption for Data on Chronic Hepatitis B

	Chi-square	**P-value**
Global test for the CPH model	10.56	0.2278

Source: Computed using STATA

Harrell's C Concordance Statistic Test

Table 3.8: Harrell's C concordance statistic for chronic hepatitis B data

Harrell's C = (E + T/2) / P = 0.8450
Somers' D = 0.6899

Source: Computed using STATA

Model Adequacy Checking Using Cox–Snell Residual Plots

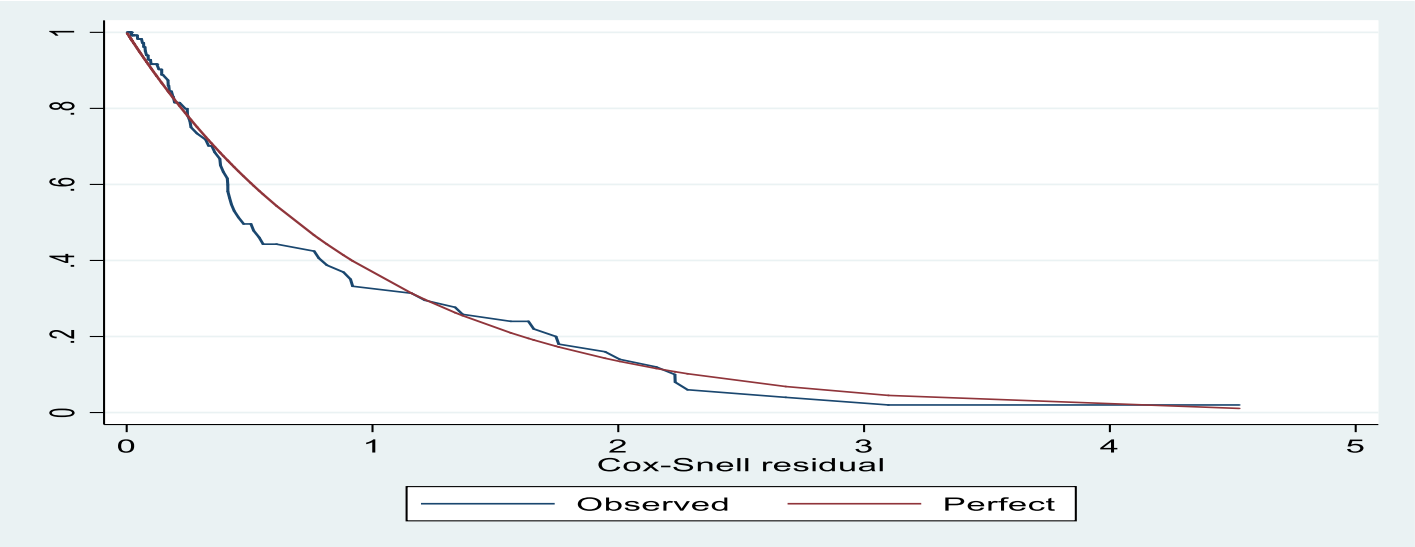

FIGURE 4.5: ***The Cox-Snell Residuals***

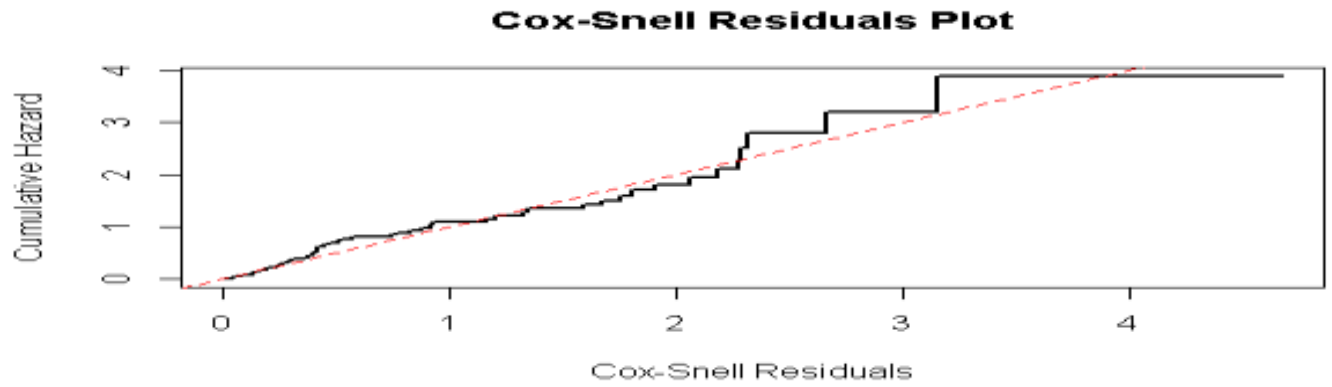

FIGURE 4.6: ***The Cox-Snell Residuals***

4.0 Discussion of the Findings

Model diagnostics, including the proportional hazards assumption test and the Cox-Snell residual plot, confirmed that the model fits the data well and meets key assumptions. Overall, the model demonstrated good predictive performance (Harrell's C = 0.845), and no violation of proportional hazards assumptions was detected. The Kaplan–Meier survival analysis and log-rank test revealed statistically significant differences in survival distributions among subgroups. The results from the Cox proportional hazard model for the chronic hepatitis B dataset revealed that older age was a major risk factor, aligning with the findings of Liang (2023) and Chen (2006), who reported that advanced age increases susceptibility to disease progression and mortality. Similarly, advanced fibrosis or cirrhosis strongly reduced survival, corroborating the findings of studies by Chen (2024) and Fattovich et al. (2008). The presence of comorbidities, such as HIV and diabetes, further compounded the mortality risk, consistent with the Danish Nationwide Cohort Study (2024). The most encouraging finding was the protective effect of antiviral therapy, particularly tenofovir, which reduced the mortality risk by 77%. This result is consistent with those of Marcellin et al. (2013) and Cho et al. (2019), who reported improved histological outcomes and reduced liver-related mortality with tenofovir treatment. Although gender and AST levels are marginally significant, their positive association with hazard suggests possible clinical importance, as reported by Hu et al. (2023) and Lo Re et al. (2019). Overall, the findings emphasize the importance of early screening, timely treatment initiation, and integrated management of comorbidities to improve HBV outcomes in Nigeria.

5.0 Conclusion

The Cox proportional hazards model identified age, fibrosis stage, comorbidities, and antiviral therapy as significant determinants of survival among patients with chronic hepatitis B. Older patients face a higher risk of adverse outcomes, and advanced liver disease and comorbid conditions markedly increases risk, whereas antiviral therapy substantially improves survival prospects. Although sex and AST levels showed positive associations, their effects were marginally significant, whereas baseline ALT and viral load did not significantly affect survival.

6.0 Recommendations

Based on the findings of this study, the following recommendations are proposed:

i. Implement routine HBV screening programs to facilitate early detection, particularly in high-risk groups.
ii. Expand access to affordable antiviral therapy, with tenofovir as the first-line treatment.
iii. Develop integrated care systems for managing comorbidities, such as HIV and diabetes.
iv. Enhance public awareness campaigns on HBV transmission, prevention, and treatment adherence.
v. Conduct multicenter research on validate findings and explore additional prognostic factors in Nigerian populations.

Ethical Consideration

Ethical approval was obtained from the Ethics Committee of the Health Research, Federal Medical Centre, Nguru, Yobe State. The patient confidentiality and data protection guidelines were strictly followed.

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