STAGE-SPECIFIC TREATMENT AND CLINICAL OUTCOMES OF PATIENTS WITH HEPATOCELLULAR CANCER AT THE UNIVERSITY COLLEGE HOSPITAL, IBADAN: A 5-YEAR REVIEW

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Submission Date: 14th Jan., 2025
Date of Acceptance: 29th Mar., 2025
Publication Date: 31st Mar., 2025

ABSTRACT

Background: **Hepatocellular carcinoma (HCC) is associated with high mortality, ranking third among cancer deaths. This study aimed to spotlight the risk factors, treatment modality and clinical outcomes over a 5-year period in our hospital.**

Methodology: **This retrospective study was done at the University College Hospital, Ibadan. All the patients with HCC diagnosed between 1st January 2019 and 31st December 2023 had their demographics, clinical information, and investigations collected. The outcome was overall survival, defined as time from diagnosis till death or lost to follow up. Data obtained was analyzed using SPSS version 20.**

Results: **A total of 138 patients were studied, 117 males (85%) and 21 females (15%). The median age was 46 years (IQR 14). Hepatitis B Virus infection was the main risk factor, found in 102 patients (73.9%). Among males, 35% took alcohol. Three patients (2.2%) with Barcelona Clinic Liver Cancer stage A, 2 underwent surgical resection, while the other one had palliative care. Of six (4.3%) stage B patients, two had levantinib, one of which also had TACE and four had palliative care only. Ten of the sixty-three patients with stage C (45.7%) received chemotherapy, while all 64 (46.4%) in stage D received supportive care. Two (1.4%) unclassified patients received symptomatic treatment. Median survival times were 1.2 months for palliative care, 3 months for chemotherapy, and 18 months for resection (P < 0.005).**

Conclusion: **Hepatitis B Virus was the main risk factor for HCC in our environment. Hepatic resection offered the best opportunity for survival.**

Keywords: Hepatocellular carcinoma, Risk factors, HBV, Resection, Chemotherapy, Liver cirrhosis.

INTRODUCTION

Liver cancer is the sixth most common cancer but the third leading cause of cancer deaths globally. A staggering 905, 677 cases were reported globally in the year 2020 and it is projected to reach one million annually by 2025. [1, 2] Developing countries are disproportionately affected when compared to their developed counterparts. The burden of the disease is particularly high in Asia and Africa.[3]

Eighty percent of all cases of hepatocellular carcinoma (HCC) were diagnosed predominantly from low- and middle-income countries, most especially Sub-Saharan Africa (SSA) and South-East Asia. [4] The age-standardized incidence rate for SSA ranges between 4.8 to 8.3 per 100, 000 person-years with West Africa having the highest incidence rate.[5] Liver cancer is the second most common cancer in men and the third cause of cancer mortality in women in SSA. There were 38, 629 new cases in the year 2020, and 36, 592 deaths were reported. It was also the second most common cause of cancer deaths in 11 countries in SSA.[4,6]

The incidence rate of HCC in Nigeria is estimated to be around 8.4 per 100, 000 persons and the mortality associated with the disease mirrors the age-adjusted incidence rate. The major reason responsible for this high mortality rate is late presentation.[7] HCC is more preponderant among young adults (median age at diagnosis is 45 years) which is in stark contrast to what is observed in high-income countries where it is more often diagnosed in older age.[7, 8]

The Barcelona Clinic Liver Cancer (BCLC) staging is the most commonly used algorithm to stage and decide on treatment that is best for a particular individual with hepatocellular carcinoma.[9-10] This staging is based on performance status of the patient, liver function as well as tumour burden. Five stages have been described; Stage 0 is very early stage, Stage A is

early stage, Stage B is intermediate stage, stage C is advanced stage and stage D is terminal stage.[10] The first two stages are treated with curative intent through ablation, resection or liver transplantation. Stage B patients may benefit from either, transarterial chemo-embolization, transarterial radioembolization or systemic treatment. Stage C is treated with systemic therapy while Stage D are only given palliative care.[11] Optimal treatment of patients with hepatocellular carcinoma remains a global challenge particularly in low-income countries. Most HCC patients cannot afford standard treatment in Sub-Saharan Africa. This is in addition to the inadequacy of infrastructure and personnel with requisite expertise in most communities.[4,5,9]

In a meta-analysis of HCC cases in sub-Saharan Africa, out of 3,989 patients identified from 15 countries, only 6% had treatment with curative intent in mind and no single patient had any of the newer agents that are now the mainstay of treating unresectable tumours.[4] In a recent work that looked at presentation and prognosis of HCC done in Lagos and Jos, none of the study participants had any form of stage-specific treatment other than supportive care. This was attributed to high costs and accessibility issues.[7] There is paucity of data on stage-specific treatment of HCC in Nigeria.

In this study, we aimed to determine the risk factors, level of stage-specific treatment and clinical outcomes of patients diagnosed with HCC over a 5-year period at the Nigerian premiere teaching hospital, the University College Hospital, Ibadan.

METHODOLOGY

The study design was retrospective involving patients with HCC diagnosed and managed over five years between January 1st, 2019, and December 31st, 2023. Ethical approval (NHREC/05/01/2008a.) was obtained from the Joint UI/UCH Ethical Committee. The record files were reviewed to obtain demographic and clinical information. Specifically, each patient's age, gender, past medical history, findings on physical examination, results/reports of investigations, treatments instituted as well as treatment outcome were documented in a specially prepared format. In addition, Barcelona Clinic Liver Cancer staging as well as Child Pugh class were inferred based on available radiological, biochemical and clinical information. Overall survival was defined as time from diagnosis to death or loss to follow-up. Data obtained were analyzed using the Statistical Package for Social Sciences (SPSS) software version 20.

RESULTS

A total of 138 case record files were identified: 11 (7.9%) in 2019, 13 (9.4%) in 2020,10 (7.2%) in 2021, 49 (35.5%) in 2022, and 55 (40.0%) in 2023. There were 117 (85%) males and 21 females (15%) (P-value = 0.000). The average age for women with HCC was 54.8 ± 14 years while for men it was 46.2 ± 11.3 years (P-value = 0.002). Hence, HCC is more frequently diagnosed in younger males than in females, who are not only fewer but also tend to be diagnosed at a significantly older age. Table 1 shows the demographic and clinical information of HCC cases. Table 2 shows age distribution and laboratory investigations.

Table 1: Demographics, clinical features and risk factors among 138 patients with Hepatocellular Carcinoma

VARIABLE	Frequency (%)	Chi-square (P value)
Gender		
Male	117 (85%)	45.4 (0.00)
Female	21 (15%)	
Marital Status		
Single	16 (11.6%)	175.6 (0.00)
Married	119 (86.2%)	
Widow	3 (2.2%)	
Religion		
Christianity	73 (52.9%)	66.9 (0.00)
Islam	64 (46.4%)	
Traditionalist	1 (0.7%)	
Tribe		
Yoruba	125 (90.6%)	316.6 (0.00)
Igbo	6 (4.3%)	
Hausa	3 (2.2%)	
Others	4 (2.9%)	
Clinical features		-
Abdominal pain	93 (67.4%)	
Weight loss	91 (65.9%)	
Ascites	79 (57.2%)	
	29 (21.0%)	
Encephalopathy	13 (9.4%)	
UGIB	11 (8.0%)	
Fever		
Number of Risk factors		
Male (n = 117)		10.5 (0.00)
0 – 1	76 (65.0%)	
≥ 2	41 (35.0%)	
Female (n = 21)		
0 – 1	21 (100%)	
≥ 2	0 (0.0%)	
Specific risk factors		
HBsAg	102 (72.9%)	246.5 (0.00)
HBsAg-/Anti-HBc T+	4 (2.9%)	
Anti-HCV	7 (5.1%)	
Alcohol	41 (29.7%)	
Tobacco	12 (8.7%)	
No traditional risk factors	10 (7.2%)	
Uncertain*	13 (9.4%)	

*Anti-HBc T; Anti-HBe Total, UGIB; Upper GastroIntestinal Bleeding, * Either HBsAg or Anti-HCV status unknown*

Table 2: Age distribution and laboratory parameters of 138 patients with HCC

VARIABLE	Mean ± SD	T- test (P value)
Age		
Male	46.2 ± 11.3	-3.09 (0.00) *
Female	54.8 ± 14.0	
Overall	47.5 ± 12.1	
AFP		
Male	124398.6 ± 244331.2	0.95 (0.343)
Female	62785.2 ± 202349.7	
Overall	115270.7 ± 238735.3	
BIOCHEMICAL TESTS		-
AST (IU/mL)	305.6 ± 335.0	
ALT (IU/mL)	92.8 ± 85.0	
GGT (IU/mL)	430.0 ± 263.6	
ALP (IU/mL)	304.5 ± 197.4	
TOTAL BILIRUBIN (mg/dl)	5.6 ± 6.3	
DIRECT BILIRUBIN (mg/dl)	4.6 ± 5.6	
TOTAL PROTEIN (g/dL)	7.7 ± 1.2	
ALBUMIN (g/dL)	3.1 ± 0.7	
INR	1.5 ± 0.5	
HAEMATOLOGICAL TESTS		-
MCV (fL)	80.8 ± 7.9	
PCV	31.6 ± 7.7	
WBC (/mm^3)	9365.0 ±4561.9	
Neutrophil (%)	70.9 ± 11.1	
Lymphocyte (%)	18.9 ± 9.4	
Eosinophil (%)	1.3 ± 1.7	
Monocyte (%)	8.5 ± 3.0	
Platelet count X 10 ^{9} (/mm^3)	244.6 ± 124.2	

*AFP: Alpha-fetoprotein; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; fL: FemtoLiter GGT: Gamma glutamyl transferase; INR; International normalized ratio; MCV: Mean Corpuscular Volume; PCV: Packed Cell Volume; WBC; White Blood cell count; * statistically significant (P < 0.05)*

Admission pattern

Ninety-three (67.4%) were admitted for various reasons-of which the top four were hepatic encephalopathy (25.8%), severe abdominal pain (25.8%), tense ascites (20.4%), and upper gastrointestinal bleeding (14.0%). Duration of admission ranged between 1 - 100 days, with a mean of 15.7 ± 15.2 days.

Risk factors

Hepatitis B surface antigenemia was demonstrated in 102 (73.9%), and evidence of previous

exposure to hepatitis B viral infection was demonstrated in another 4 (2.9%) individuals as they were serologically positive for only anti-HBc total, while hepatitis C virus was considered associated risk factor

Table 3: Characteristics of 115 patients with cirrhotic and non-cirrhotic HCC

VARIABLE	Cirrhotic HCC	Non-Cirrhotic HCC	Chi-square (P value)
Frequency (%) N = 115	106 (92.2%)	9 (7.8%)	0.00*
Mean age ± SD	47.4 ± 12.1	50.7 ± 15.1	0.547
Gender			
Male	86 (74.8%)	9 (7.8%)	0.356
Female	20 (17.4%)	0 (0.0%)	
HBsAg status (N = 107)			
Positive	84 (78.5%)	5 (4.7%)	.042*
Negative	14 (13.1%)	4 (3.7%)	
Mean AFP ±SD	106, 450.7 ± 235,090.2	17,872.4 ± 20, 526.9	0.001*
Outcome (months)			
Mean survival	1.8 ± 1.7	7.1 ± 8.8	0.000*
Median survival	1.2	2.0	0.025*
Range	0.5 - 14	0.5 - 19	-

*AFP: Alpha-fetoprotein; SD: Standard deviation; * statistically significant (P < 0.05)*

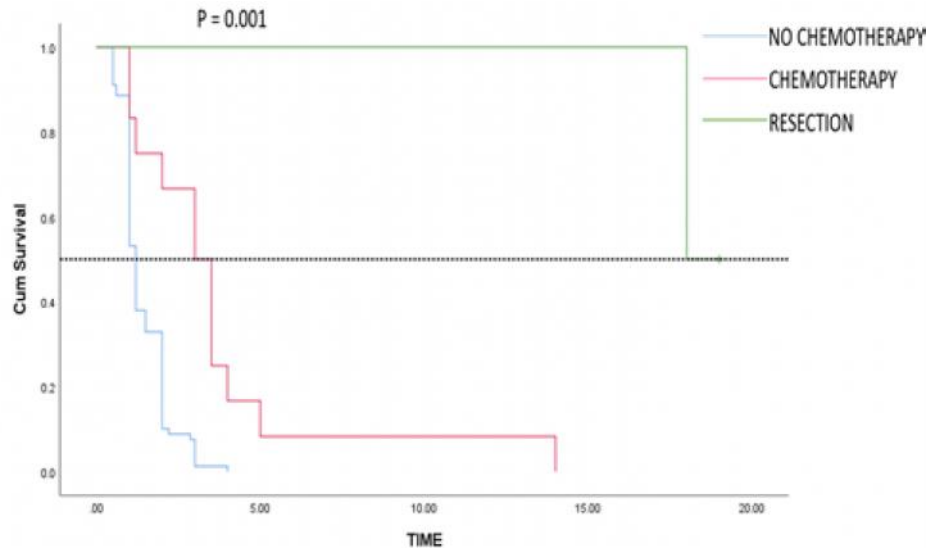

Figure 1: Kaplan-Meier survival analysis of 3 groups of patients with HCC; those who had resection (green line), chemotherapy (red line) and those who had only supportive care (blue line). The difference in outcomes was statistically significant with P-value of 0.001.

in 7 (5.1%) patients. In addition, the male patients had alcohol consumption and tobacco use in 35% (41/117) and 10.3% (12/117) respectively as shown in Table 1.

Cirrhotic and Non-Cirrhotic HCC

Status of cirrhosis obtained from either abdominal ultrasound scan or triple-phase computed tomography scan was documented in 115 (83.3%) patients of all the 138 patients with HCC as shown in Table 3, with 106 (92.2%) cirrhotic HCC while 9 (7.8%) had non-cirrhotic HCC. The mean AFP was considerably higher in patients with cirrhotic HCC (106, 450.7 ± 235,090.2ng/mL) compared to 17,872.4 ± 20, 526.9 ng/mL for non-cirrhotic HCC patients (P-value =

Table 4: Barcelona clinic liver cancer (BCLC) staging and treatment in 130 patients with HCC

BCLC stage and treatment modality	Frequency (%)	Median survival (Range) in months
A (n = 3)		18.0 (18 – 30)
Resection	2 (1.4%)	
BSC	1 (0.7%)	
B (n = 6)		2.0 (0.5 – 3.5)
Levantinib	1 (0.7%)	
Levantinib + TACE	1 (0.7%)	
BSC	4 (2.9%)	
C (n= 63)		
Atezolizumab-bevacizumab	1 (0.7%)	2.0 (0.5 – 14)
Capecitabine	1 (0.7%)	
Cyclophosphamide	2 (1.4%)	
Levantinib	2 (1.4%)	
Sorafenib	4 (2.9%)	
BSC	53 (38.4%)	
D (n = 64)		1.0 (0.5 – 4)
BSC	64 (46.4%)	
Unclassified (n = 2)		
BSC	2 (1.4%)	1.0 (-)
TREATMENT SUMMARY		
Resection	2 (1.4%)	18.0 (18 -30)
Sorafenib	4 (2.9%)	4.0 (2 – 14)
Atezolizumab-Bevacizumab	1 (0.7%)	3.5 (-)
Levantinib	3 (2.1%)	3.0 (1 – 3.5)
Levantinib + TACE	1 (0.7%)	3.0 (-)
Capecitabine	1 (0.7%)	1.2 (-)
Best Supportive treatment	124 (89.9%)	1.2 (0.5 – 5)
Cyclophosphamide	2 (1.4%)	1.0 (1 -3.5)

BSC: Best supportive care, TACE: Trans-arterial chemoembolization

0.01). The mean survival was 1.8 ± 1.7 months for those with cirrhosis while it was 7.1 ± 8.8 months for non-cirrhotic HCC (P-value = 0.00). There was no age or gender difference in the two groups. However, HBsAg was commoner in cirrhotic HCC (84/98) compared to non-cirrhotic HCC (5/9) with P = 0.042. Table 3 shows the clinical profile of cirrhotic and non-cirrhotic HCC.

Treatment

In Table 4, one hundred and twenty-four patients (89.9%) of the patients had neither chemotherapy nor were qualified for surgical intervention. Three patients (2.2%) had BCLC stage A, 2 of which underwent surgical resection, while the other one received supportive care only. Of six (4.3%) stage B patients, two were treated with levantinib, one of which had received prior transarterial chemoembolization at another facility while the remaining four individuals with stage B had only supportive care. For patients with stage C, 10 of 63 (45.7%) received anticancer agents, while the rest (53 patients) and all 64 (46.4%) in stage D received palliative care only. Two (1.4%) patients were unclassified but received symptomatic treatment. Therefore, the level of stage-specific treatment was 66.7% in those with stage A disease, 16.7% in those with stage B disease, 15.9% for stage C and 100% for stage D. Overall, fifty-nine (43.4%) patients did not have stage-specific treatment.

Survival outcomes

The median survival time for BCLC stage A, B, C and D were 18months, 2 months, 2 months and 1 month respectively (P < 0.001). The median survival was 18 months for those who had resection, 3 months for those that had any form of anticancer agent while the median survival was only 1.2 months for those who were managed with supportive care only. Figure 1 shows the Kaplan-Meier Curve of patients with HCC at UCH, Ibadan. In this study, the two-year survival rate was 0.7%, with only one patient who underwent resection remaining in follow-up care after 2.5 years.

DISCUSSION

The findings of this study shows that viral hepatitis B and C remain the driver for hepatocellular carcinoma with 75.8% and 5.1% of the patients having evidence of HBV or HCV infection respectively. HBV as a risk factor for HCC was higher in this study group when compared to that of previous studies, 52% - 55%, in Jos, Lagos and Zaria where hepatitis virus infections have always been noted as a key etiologic factor.[7, 13] Furthermore, trends in many North African countries, particularly in Egypt is somewhat different. Hepatitis C infection is the predominant risk factor for hepatocellular carcinoma in this region where 84% of HCC cases have HCV infection compared to the paltry 5.1% seen in this study.[14] The plausible explanation is related to the higher national prevalence of HBV (8.1%) when compared to HCV (1.1%) in Nigeria.[15] Furthermore, it appears more patients had their HBV and HCV status documented in our own study.

Most of the patients presented with advanced disease with poor survival outcomes, however, those who had early staged disease and had resection survived for considerably longer time when compared to other treatment groups. More than 4 in 10 patients did not have appropriate stage-specific treatment. Additionally, the use of newer targeted therapy was abysmally low. The use of chemotherapy in the study population is low with only 12 (8.7%) patients. Despite the availability of first-line targeted therapies for HCC, only one patient had first-line chemotherapy (Atezolizumab-Bevacizumab combination). The main reason for this is the prohibitive cost of these medications for HCC coupled with the fact that most of the patients pay out of pocket. Nevertheless, the use of targeted therapies in this study is considerably higher than what was reported in other studies.[14] The reasons for this may be due to better access to these drugs, physicians' counseling on possible benefits and willingness of patients to accept such treatments.

Most patients in our study cohort were seen at BCLC stages C (45.7%) and D (46.4%), indicating that most patients are diagnosed at advanced stages. This explains why most were not eligible for potentially curative interventions (resection, transplant and locoregional therapy) but rather chemotherapy and palliative care only. The situation is diametrically different in the developed climes, where HCC patients generally present early with a high proportion able to undergo surgery and/or receiving potent chemotherapeutic agents.[5] Late presentation and/or inability to institute surgical or pharmacological interventions invariably resulted in deaths of the affected patients. Most patients presented late in advanced HCC (87.2%), on a background liver cirrhosis (92.2%), with significant liver dysfunction culminating in a more challenging therapeutic landscape which is similar to what has been reported Gambia[16]

Two-year survival in this study was 0.7% with only one patient who had resection making it beyond the 2-year mark. In similar circumstances and other parts of Nigeria, poor prognosis has been reported for example, in Jos the median survival was 2.3 months and in Osun state, the median survival was less than a month.[7, 17] It is noteworthy that the patients in these other studies received no targeted therapy.

One of the patients had trans-arterial chemoembolization that was done at another center in Lagos. This center is the only place in the whole country to the best our knowledge to be capable of delivering such locoregional therapy. [18]The prohibitive expense associated with this mode of treatment particularly for BCLC stage B HCC, contributed to the low uptake in this study.

Two patients (1.4%) had resections with median survival of 18 months while 12 (8.7%) patients had anticancer agents with median survival of 3 months. This is in stark contrast to what was reported in Lagos and Jos where none of the patients (except those with stage D disease) had any stage-specific treatment. [7] None of the patients had other curative modalities such as transplantation, or ablative procedures which are currently not readily available in the country. In contrast, patients with HCC in South Africa have access to liver transplantation.[19] Noteworthy is that the only curative treatment available is resection, and it offers the best survival rate at 2 years in our experience.

Limitation to the study was lack of complete data, particularly in the first three years where case note retrieval rate was low. However, it is possible that COVID-19 may have likely played a role. Also, industrial actions embarked by health workers particularly in the year 2020 could also explain the low turnout in that particular year.

CONCLUSION

The stage-specific treatment of HCC at the Nigerian premiere hospital, University College Hospital Ibadan is far from being optimal. Early detection and curative treatment (surgical resection) had a better chance of two-year survival compared to other treatment modalities. This suggests that a good surveillance system in individuals at risk, particularly those with chronic viral hepatitis may help in identifying patients with HCC at an early-stage that may be amenable to curative surgical intervention.

Conflict of interest and sponsorship: The authors declared no conflict of interest. The authors received no financial assistance or grant for this work.

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