

## Characteristics of Hepatocellular Carcinoma in Two Tertiary Hospitals in Nigeria - Has anything Changed?

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### INTRODUCTION

Hepatocellular carcinoma (HCC) is a global health problem accounting for 5.6% of all human cancers although less developed countries are disproportionately affected.<sup>[1]</sup> It is the fifth most common cancer in men (554,000 cases) and the ninth in women (228,000 cases). In both sexes, it is the sixth most common cancer responsible for 748,000 new cases of cancer annually and the third leading cause of cancer related death exceeded only by cancers of the lung and stomach.<sup>[2]</sup> The incidence of HCC is increasing both in the developed and developing countries. This has been attributed to the rising prevalence of its risk factors; chronic hepatitis B and C infection, alcohol abuse, non-alcoholic fatty liver disease (NAFLD) associated with type 2 diabetes and obesity.<sup>[3-5]</sup> HCC is characterized by several epidemiological features including dynamic temporal trends, variation among geographic regions, racial and ethnic groups and the presence of several preventable risk factors.<sup>[6]</sup> Although HCC was one of the first cancers to be linked epidemiologically to hepatitis B virus which is preventable, its incidence remains high in regions of the world where the virus is endemic.<sup>[7]</sup> In 2002, it was estimated that 82% of all liver cancers occurred in the developing countries of south-eastern Asia and sub-Saharan Africa. In these regions, majority of HCC tend to occur in persons with chronic hepatitis B virus infection and to a lesser extent in patients with chronic hepatitis C virus infection.<sup>[1]</sup> Other potential contributory factors include high dietary exposure to aflatoxin, a common

contaminant of foodstuffs such as nuts, grains and legumes, dietary iron overload, alcohol abuse and non-alcoholic steato-hepatitis (NASH) associated with type 2 diabetes and the metabolic syndrome.<sup>[8]</sup>

The prognosis of HCC is still poor with an annual case-fatality ratio of 0.93 which is the highest for any malignancy.<sup>[2]</sup> This is more so in developing countries where late presentation coupled with paucity of diagnostic and interventional facilities have rendered the tumor untreatable.<sup>[9]</sup> This is in contrast to what obtains in the developed countries where diagnosis of the tumor in the early stages makes institution of intention-to-cure therapies possible with 5-year survival rates approaching 70-80%.<sup>[10-11]</sup> Over the past decade, advances in understanding of risk factors for hepatocellular carcinogenesis, medical imaging, interventional radiology and surgical techniques including liver transplantation have resulted in considerable opportunities for HCC prevention, surveillance, early detection and treatment with improvement in prognosis.<sup>[1],[12]</sup>

Several reports on the epidemiology of HCC in Nigeria in the last three decades suggested a predilection for males in the 3<sup>rd</sup> and 4<sup>th</sup> decades of life who are chronically infected with hepatitis B virus.<sup>[13-16]</sup> The tumour is characterized by late presentation with the mean duration of appearance of symptoms to death of approximately 20 weeks. Palliative care is the norm as patients are too ill for any curative intervention.<sup>[16]</sup>

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**AIMS AND OBJECTIVES**

The aim of this study is to determine the characteristics of HCC in two tertiary healthcare institutions in Nigeria in the 21<sup>st</sup> century compare with previous studies and highlight changes in presentation and management or lack of it.

**SUBJECTS, MATERIALS AND METHODS**

This was a retrospective study to assess the clinical, laboratory and radiological characteristics of HCC in two tertiary health centers in Nigeria over a four year period. A structured questionnaire was used to abstract information on the age, gender, symptoms at presentation, and results of investigations and mode of diagnosis of HCC in all patients seen at the University of Calabar Teaching Hospital, Calabar and Dalhatu Araf specialist hospital, Lafia from January 2012 to December, 2015. Data was aggregated and all identifying information removed. Ethical clearance was obtained from the Ethics committee of the Dalhatu Araf specialist hospital and ratified by

the University of Calabar Teaching Hospital Ethics committee.

**DATA ANALYSIS**

Data generated from the study was analyzed using the Statistical Package for Social Sciences (SPSS) version 20. . Continuous variables were presented as means and standard deviation (SD) while categorical variables were presented as percentages. Chi square and odds ratio at 95% confidence interval was used to test for association between variables. Statistical significance was established as  $p < 0.05$ .

**RESULTS**

A total of 100 patients with HCC were analyzed. Their age ranged from 12- 90years with a mean age of  $43.15 \pm 16.3$  years and a median age of 40 years. They were 70 males and 30 females with M: F ratio of 2.3: 1. The mean age of males was  $43.16 \pm 15.6$  years and that of females was  $43.2 \pm 18.2$  years. The age group most affected is 30 -49 age group as shown in table 1. The difference in age and sex distribution was not statistically significant ( $p=0.16$ ).

Table 1- Age and Sex distribution of the study population

Age group (Years)	Sex		Total (%)
	Male (%)	Female (%)	
<20	3.1	3.1	6.1
20-29	11.2	6.1	17.3
30-39	17.3	5.1	22.4
40-49	17.3	3.1	20.4
50-59	7.1	8.2	15.3
60-69	9.2	2.0	11.2
70 and above	4.1	3.1	7.1
Total	69.4	30.6	100

$X^2 = 9.116$        $p = 0.16$

The diagnosis of HCC was made based on typical clinical features of tender nodular hepatomegaly with or without bruit, easy satiety, weight loss and abdominal ultrasonography in the majority of patients (Table 2).

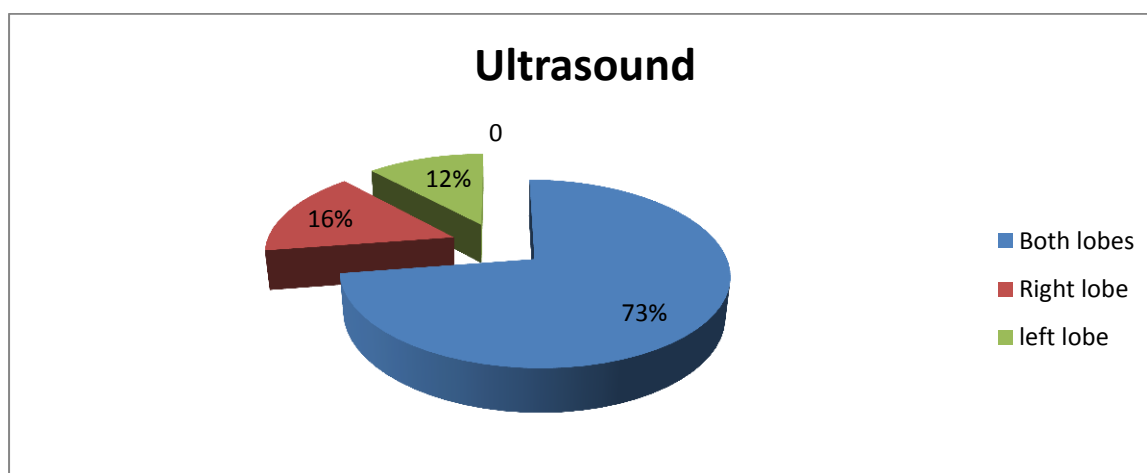
Table 2- Mode of diagnosis

Mode of diagnosis	Frequency (%)
Ultrasound plus clinical features	72
Clinical features only	13
Liver biopsy	8
CT-scan	5
FNAC	2

CT-scan – Computer tomographic scan, FNAC- Fine needle aspiration cytology

Of those who had ultrasonography, 72.6% had lesions in both lobes of the liver, 15.5% in the right lobe and 11.9% in the left lobe. The nodules were reported as multiple with a mean size of 8.5cm (Fig. 1).

Figure 1- Lobes of the liver affected on ultrasonography



Mean size of lesions = 8.5cm

Hepatitis B virus (HBV) was positive in 48% of the patients, 22% had positive hepatitis C virus (HCV) result and 3% had HBV/HCV co-infection. Significant alcohol intake was documented in 38% of patients out of which 31.5% were HCV positive and 36.8% were HBV positive. The mean age of patients

who were HBV positive was 38.2±15.9 years while the mean age of patients who were HCV positive was 48.6 ±18.9 years. HCC occurred at an earlier age in patients who were HBV positive compared to HCV positive patients and the difference was statistically significant for HBV but not for HCV (Table 3).

Table 3-Association between Age , HBV and HCV infection

Risk factor	Age		Chi sq.(p-value)	OR (95% CI)
	≤ 40years N(%)	>40 years N(%)		
HBV positive	31(64.6)	17(35.4)	6.244(0.012)	1.69(1.097-2.603)
HCV positive	9(40.9)	13(59)	0.646(0.42)	0.734(0.343-1.569)

OR= Odds ratio, CI = Confidence interval

The value of Alpha-feto-protein ranged from 0.2-19,640ng/ml with a mean of 1714.6 ±4025ng/ml. The mean Child-Pugh (C-P) score was 7.8±2.3 and the mean Model for end-stage liver disease (MELD) and Model for end-stage liver disease –sodium (MELDNa) scores were 15.3±6 and 17.3±7.6. The mean C-P score, MELD and MELDNa scores for males were higher than for females 8.33 vs 6.79, 16.74 vs 12.33 and 18.33 vs 14.22. The difference was statistically significant for C-P score but not for MELD and MELDNa (P = 0.04, 0.07 and 0.14 respectively). The MELDNa was slightly higher than the MELD in patients with hyponatremia. Nonetheless, there was a statistically significant correlation between the MELD and MELDNa scores (p<0.001). Categorizing patients according to C-P class at presentation, 56% were in class B, 29.3% in class A, and 14.7% in class C. For MELDNa, 44.4% had a score of 10-20, 21.6% had a score of 21-30, 22.2% had a score of less than 10 and 3.7% had a score > 30. Palliative care was offered to 97 of the patients while 3 received chemotherapy. Majority of

the patients (66.6%) were lost to follow-up and the remaining 33.4% died within one month of admission.

#### DISCUSSION

HCC remains a major cause of morbidity and mortality in Nigeria. This study showed that males are affected at least twice as much as females with no significant variation in age. This trend has not changed. It has been reported globally and in previous studies in the different regions of Nigeria.<sup>[1][12-16]</sup> Among the reasons proposed for this male preponderance include the increased androgen signalling effect of testosterone with subsequent promotion of liver cell proliferation, higher rates of exposure to environmental carcinogens especially alcohol and higher iron stores.<sup>[8][17]</sup> The majority of patients with HCC were aged 30-49 years with a mean age of 43.15 ±16.3 years. Nwokediuko et al<sup>[18]</sup> reported a mean age of 43.17 ±16.5 with a peak in the age group 20-59years in eastern Nigeria. Similar findings were also reported in northern, southern and

western regions of Nigeria.<sup>[15][19-20]</sup> In Europe and North America, HCC usually affect older person (65years and above).<sup>[1]</sup> HBV associated HCC tended to occur in persons  $\leq$  40 years when compared to HCV associated HCC ( $p=0.012$ , (OR 1.690, 95% CI 1.097-2.603) vs  $p = 0.42$ , (OR 0.734, 95% CI 0.343-1.569). Our finding was similar to what was documented among HCC patients in a recent multinational study involving Nigeria and several West African countries.<sup>[21]</sup> This has been attributed to the age of acquisition of HBV and HCV which for HBV, is through vertical and horizontal transmission at birth and early childhood (1-5years) and for HCV, is through transfusion of unscreened blood, unsafe sexual practices and intravenous drug abuse.<sup>[7][8][22-23]</sup>

Hepatitis B virus infection was found to be the most common risk factor for HCC in this study with a prevalence of 48%. It was followed by alcohol (38%) and HCV (22%). Other studies in Nigeria have also shown HBV to be the most common risk factor for HCC with prevalence rates ranging from 49-80%.<sup>[24-25]</sup> In Enugu, common risk factors for HCC were reported to be HBV (61.5%), alcohol (59.8%) and HCV (11.6%).<sup>[18]</sup> In Maiduguri, HBV, HCV and alcohol consumption was reported in 67%, 18% and 9% respectively of a cohort of 100 HCC patients.<sup>[19]</sup> HBV induces chronic necro-inflammation in the liver leading to cirrhosis, a harbinger of malignant transformation. The viral DNA can directly integrate into the host DNA leading to *cis*-activation of hepatocellular genes with mutagenic tendencies. In addition, the x-protein has transcriptional activities and has been shown to suppress the activities of the p53 tumor suppressor gene.<sup>[12]</sup> Thus; persons with HBV infection are 100 times more likely to develop HCC than non-infected persons with annual incidence rates increasing from 0.5% in non cirrhotic patients to 2-6% in cirrhotic patients.<sup>[26]</sup> Alcohol and HCV infection are of less significance in the aetiology of HCC in Nigeria when compared to western countries.<sup>[1][7]</sup>

Majority of the patients were diagnosed based on clinical features and plain abdominal ultrasound. This is only possible in the presence of advanced disease. As in our study, other studies in Nigeria had reported that patients with HCC present late with features of advanced disease such as right upper quadrant mass, abdominal swelling and weight loss.<sup>[9][15][18-20]</sup> In such instances, it is easy to make diagnosis without sophisticated equipments and invasive tests. However, in the early stages of the disease when the tumour is asymptomatic, diagnosis is based on typical findings on contrast imaging studies usually computer tomographic scan (CT-scan), magnetic resonance imaging (MRI) or ultrasound. The contrast is necessary to enhance the tumor which are usually small initially (2-3cm) and highly vascular. A liver biopsy is only required in tumours less than 2cm and

those that fail to show the typical enhancement and wash-out during the arterial and delayed phase of contrast imaging. These asymptomatic tumors are usually detected during surveillance of at risk population and are amenable to therapy with curative intent such as surgical resection and liver transplantation.<sup>[27-28]</sup> None of the patients in this study was in a surveillance program. To the best of our knowledge, no study in Nigeria had been conducted among patients in a surveillance program for HCC. Some of the reasons for the lack of surveillance include; lack of awareness of HBV/HCV status of the general population and inadequate evaluation of persons with chronic hepatitis B/C virus infection due to out-of-pocket payment for investigations and drugs.<sup>[7]</sup> Thus, most patients with chronic viral hepatitis B/C are unwilling or rather unable to carry out repeated investigations and prolonged treatment when they are asymptomatic.

This study showed that most of the patients were in C-P class B and MELDNa category of 10-20. We found only two studies in Nigeria that have categorized patients with chronic liver disease (CLD) including HCC according to C-P and MELD scores and none for MELDNa scores. These studies reported that majority of the patients presented in C-P class C and higher MELD scores and therefore are unlikely to benefit from therapies with the intention-to-cure or down-grade the tumor.<sup>[29-30]</sup> Our study showed marginal improvement. However, this has not translated to improved prognosis as 97% of the patients received only palliative care, 3% received chemotherapy and majority were lost to follow-up. This is similar to what was reported by Ndububa et al<sup>[15]</sup> in Ile-Ife, western Nigeria. In that study, 96.1% of their patients with HCC were offered only symptomatic treatment, 3.25% had chemotherapy and 59.8% were either discharged against medical advice or lost to follow-up. The reason for the dismal outcome of HCC in Nigeria is postulated to be multifactorial. First is the inability of clinicians to adequately evaluate and treat their patients with chronic hepatitis and place them on surveillance for HCC. A study on the 'challenges in the management of chronic HBV in West Africa; the Clinicians perspective' showed that clinicians were willing to properly evaluate and treat their patients, however, resource constraint and high patient drop-out from treatment was a major challenge.<sup>[31]</sup> Secondly, most if not all the centres in Nigeria lacks the necessary manpower and facilities for loco-regional therapies such as radiofrequency ablation and trans-arterial embolization of the tumor. A few offer percutaneous ethanol injection and surgical resection but none offers liver transplantation. The implication is that patients who would have benefitted from such therapies are offered only palliative care and left to deteriorate further. Lastly, there is evidence that knowledge of hepatitis B virus, a major risk factor for

HCC, is low amongst the lay adult population. Hence, harmful practices that predispose to the acquisition of the virus are prevalent and vaccine uptake is very low.<sup>[32]</sup> Yang et al<sup>[1]</sup> had noted that in resource poor countries such as Nigeria, effort at curbing the menace of HCC should be focused on prevention and adequate treatment of persons chronically infected with hepatitis B virus.

### CONCLUSION

HCC still affects young Nigerians in the 3<sup>rd</sup> and 4<sup>th</sup> decade of life with HBV infection being the most common risk factor. This and has been the trend in the last two decades. Patients appear to present slightly earlier than suggested by previous studies. However, prognosis is still poor because of resource constraints and lack of facilities for therapy with curative intent.

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### Competing interests

The authors declare that they have no competing interests.

### Authors' contributions

OU contributed to the design of the study, collected and analyzed data and wrote the manuscript. BR participated data collection and discussion. NO contributed to discussion and had an overview of the manuscript. NI had contributed to discussion and coordination of the study. All authors read and approved the final manuscript.

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