

SJMLS-3(1)-002

**Cytoarchitectural Pattern of Hepatocellular Carcinoma (HCC) in Ahmadu Bello University Teaching Hospital Zaria, Nigeria**Mairiga, A.A.<sup>1</sup>, Adoke, K.U.<sup>2</sup>, Zakariya, A.G.<sup>3</sup>, Ogefere, H.O.<sup>4</sup>, Ataman, J.E.<sup>5\*</sup>

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**Abstract**

Hepatocellular carcinoma (HCC) has been identified as the most frequent primary liver malignancy, mostly occurring in the context of chronic liver diseases leading to cirrhosis. Epidemiological data demonstrate the increasing incidence of HCC worldwide, mainly related to viral hepatitis and metabolic syndrome. Pathological analysis recognizes several types of HCC according to macroscopic and microscopic features. This cancer has heterogeneous geographical distribution based on the prevalence of risk factors in different parts of the world. This study determined the histopathologic pattern of diagnosed Hepatocellular carcinoma (HCC) through a twenty-year retrospective study among patients who attended Ahmadu Bello University Teaching Hospital, Zaria. One hundred and fifty-one cases were included in this study during the period under review. There were 88 males (58.3 %) and 63 females (41.7 %) in whom diagnosis of HCC was made. The age ranged between 1 year and 80 years with mean of  $40.87 \pm 3.25$ . The highest incidence was between the ages of 40 and 50 years with a mean age of  $46.25 \pm 3.21$  years. Histopathologic features of HCC cells showed nests and trabeculae of neoplastic hepatocytes often having large prominent nucleoli and numerous mitotic figures including atypical forms. With Masson's trichrome stain, the nests of neoplastic changes were delineated by fibrous bands. These neoplastic cells on immunohistochemical stain had a focal and dot like cytoplasmic staining for cytokeratin. There was no significant association between gender and mean age of patient ( $p > 0.05$ ) in this study.

**Key words:** Hepatocellular carcinoma, Cytoarchitectural pattern, ABUTH, Zaria

**Introduction**

Cancers affecting the liver may be primary or secondary (metastatic). Hepatocellular carcinoma (HCC) has been considered the commonest primary cancer of the liver (McGlynn and London, 2011; Parkin *et al.*, 2005). It is said to have a heterogenous geographical distribution determined mainly by the presence of the risk factors in different parts of the world. It is more common in Sub-Saharan Africa and South-East Asia than North America and Western Europe (Parkin *et al.*, 2005). In the Asia Pacific region, it has been reported to be among the top three causes of cancer deaths because of the high prevalence of its main aetiological factors, chronic hepatitis B and C (Yuen *et al.*, 2009; El-Zayadi *et al.*, 2005). Older age from 40 years and male to female ratio of 3:1 have been associated with its incidence in this region. Hepatitis B and C virus are undisputedly considered as the major hepatocarcinogen in Asia and Africa, where the infection is acquired early in life with higher male predisposition due to the risk factors such as genetics, infection with hepatitis C and B viruses, alcohol consumption, smoking, increased iron stores and high levels of aflatoxin markers (Colombo, 2003). In Northern Europe and the United States, HCC is said to be commonly associated with alcoholic liver disease (Hayashi and Di Bisceglie, 2005). Supporting these claims was the observation that about 80% of global cases of HCC are due to underlying chronic hepatitis B and C (Perz *et al.*, 2006). HCC has also been identified as the fifth

mainly ordinary cancer in the world as well as the most common type of primary liver tumor (Nicholas and Paul, 2003). Furthermore, attributed to it, is that it is the main common malignancy connected with poor diagnosis (Okano *et al.*, 2001). In this sense, it has been described as a multi-stage disease linked to environmental, dietary and life style factors that can even arise from a previously damaged liver or cirrhosis (Anzola, 2004; Bosch *et al.*, 2004; Fattovich *et al.*, 2004). Some associated risk factors attributed to this disease include; gender (male), alcoholism, ageing, diabetes, family history, hepatitis B and C, iron overload, obesity, alpha-1-anti-trypsin deficiency etc. (Chen *et al.*, 2006; Anzola, 2004; Bosch *et al.*, 2004; Beasley, 1988). Some cases of HCC resulting from hepatitis B without previous cirrhosis have actually been reported (Levanchy, 2004). Sometimes, precursor lesions may commence in the sequence of hepatocellular adenoma, and may occur in females using oral contraceptives or in male patients with glycogen storage disease or those on androgen treatment (Vijay *et al.*, 2015; Ronald *et al.*, 2004). Hepatocellular carcinoma has been said to range from well-differentiated to highly anaplastic undifferentiated lesions, presenting as trabecular, sinusoidal, pseudo glandular, solid or mixed of all types, but all with the common tendency to invade blood vessels with metastatic spread (Kumar *et al.*, 2005). This tumor classification histologically is further buttressed by the WHO criteria into further morphological subtypes including the compact, fibrolamellar or schirrous (Hirohashi *et al.*, 2000). Two classical pathways in cellular differentiation (Wnt-beta-catechin, Hedgehog) are said to be frequently altered in the progression towards malignancy (Bruix, 2014). The well-differentiated, clear cell and fibrolamellar tumor types as well as the presence of tumor encapsulation have been associated with better prognosis (Cillo *et al.*, 2004).

A distinct feature of HCC is the fact that prognosis is not determined only by the tumor disease but also by the severity of the underlying liver disease. Synergistic effect of alcohol and hepatitis B and /or C infection causing gradual progression of chronic liver disease to cirrhosis

and HCC has been documented reports within sub-Sahara Africa (Dunn and Shah, 2016; Mueller *et al.*, 2009). Many patients who are diagnosed with HCC have advanced disease and are only candidates for palliative care, contributing to a relatively low reported 5-year survival rates of approximately 10% (London and Mc Glynn, 2006). In high prevalence areas, many patients die within 6 months of diagnosis. There are several reports in Nigeria on the epidemiology of liver cancer (Vhritherhire *et al.*, 2016; Mustapha *et al.*, 2007; Seleye-Fubara *et al.*, 2007). Such high incidence of deaths from HCC is understandable considering the attendant high risk aetiological factors and poor surveillance approach to its early detection and management. Ladep and colleagues (2014) reported that outside East Asia, sub-Saharan Africa has the highest HCC with early risk factors such as low uptake of childhood immunization and high endemicity of hepatitis B and other environmental factors. Of significance is the pointer to even the iron pots used in brewing local beer as a potential source of iron overload. Also noted in their submission is the fungus-infected malt, a product of cereal used in the fermentation of local beer “Burukutu”. This cereal is a reported source of aflatoxin known to potentiate carcinogenicity (Ladep *et al.*, 2014). It is therefore understandable why Akinyinka *et al.*, (2001) found in their studies that the mean (SD) of presentation of HCC in children was 10.4 (3.0) years with short duration of illness before presentation, usually with poor prognosis. Since HCC in the environment is widely reported to be associated with poor prognosis, the need to demonstrate the cytological patterns commonly observed, apart from the already existing data on the socio-demographic variables related to the prevalence of HCC in the sub-region becomes imperative. Hence, this twenty-year retrospective study was carried out to determine the common cytoarchitectural pattern of HCC at the Ahmadu Bello University Teaching Hospital, Zaria, Kaduna State.

### Materials and Method

This study is a retrospective study of cases of HCC that were diagnosed at the Department of Histopathology, Ahmadu Bello University Teaching Hospital, (ABUTH) Zaria, Nigeria

between the months of January, 1993 to December, 2013. These would involve all cases which were histologically diagnosed as HCC. The source of study material was the bench registers of the Department. Clinical data such as the age and gender were extracted from the registers. Paraffin embedded tissue blocks as well as relevant slides stained with haematoxylin and eosin stains (H&E) were also retrieved from the Department. In cases where slides were missing, fresh sections were made from retrieved paraffin blocks and stained with haematoxylin and eosin stains (Drury and Wallington, 1980). A special stain used was Maisson's trichrome. Immunohistochemical stain was done using cytokeratin (CK7). Genemed protocol was adapted in the study and normal liver tissue was used as the control. Data was analyzed using SPSS version 20 with significant level put at  $p \leq 0.05$ .

The study was conducted at ABUTH, Zaria.

Zaria is a major city in Kaduna state in Northern Nigeria as well as being a Local Government Area. Formerly known as Zazzau, it was one of the original seven Hausa city-states. The city has an estimated population of about 408,198 according to the (2006 census) population reports and a total area of 300 km<sup>2</sup> (100 sq m) with density of 1,400/km<sup>2</sup> (3,500/sqm). Zaria is situated at 11.11<sup>o</sup> North latitude, 7.73<sup>o</sup> East longitude and 613 meters elevation above the sea level (Maiwada and Renne, 2007). The Hospital is located at the North- Western zone of Nigeria. Patients come from other neighboring States like Niger, Kogi and Benue.

### Results

A total number of 151 patients (88 male and 63 female) with histopathological confirmation of hepatocellular carcinoma (HCC) were registered between January 1993 and December, 2013. Their ages ranged from 1 year to 80 years (mean = 40.25

**Table 1: Percentage distribution of patients with HCC based on age groups**

Age Groups (Years)	N	All Subjects (n = 151)		N	Males (n = 88)	Females (n = 63)
		All (%)	M (%)			
0 – 9	9(5.9)		3(3.4)	6(9.5)	3.67 ± 3.06	4.50 ± 3.99
10 – 20	12(7.9)	15.25 ± 4.03	7(7.9)	5(7.9)	14.14 ± 4.06	16.80 ± 3.83
20 – 30	31(20.5)	27.71 ± 2.51	21(23.8)	10(15.8)	27.86 ± 2.22	27.40 ± 3.13
30 – 40	32(21.2)	35.09 ± 3.29	25(28.4)	7(11.1)	35.12 ± 3.31	35.00 ± 3.46
40 – 50	32(21.2)	46.25 ± 3.21	19(21.5)	13(20.6)	46.32 ± 3.33	46.15 ± 3.16
50 – 60	18(11.9)	57.28 ± 3.46	8(9.0)	10(15.8)	56.38 ± 4.03	58.00 ± 2.94
60 – 70	13(8.6)	65.69 ± 2.66	3(3.4)	10(15.8)	63.33 ± 1.53	66.40 ± 2.55
70 – 80	4(2.6)	75.50 ± 3.32	2(2.3)	2(3.2)	75.00 ± 0.00	76.00 ± 5.66

**Key**

*N* = Number of subjects

*n* = All subjects

*M* = Males

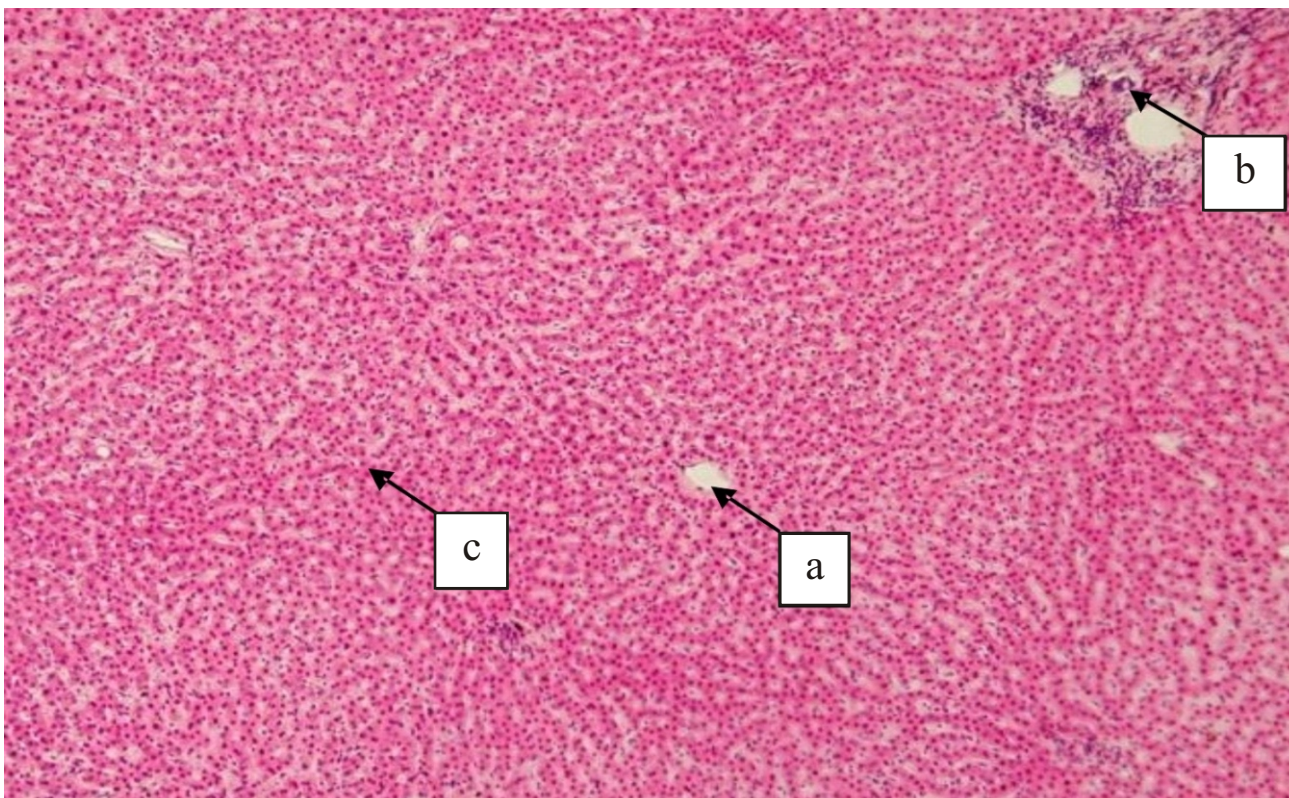
*F* = Females

*SD* = Standard Deviation

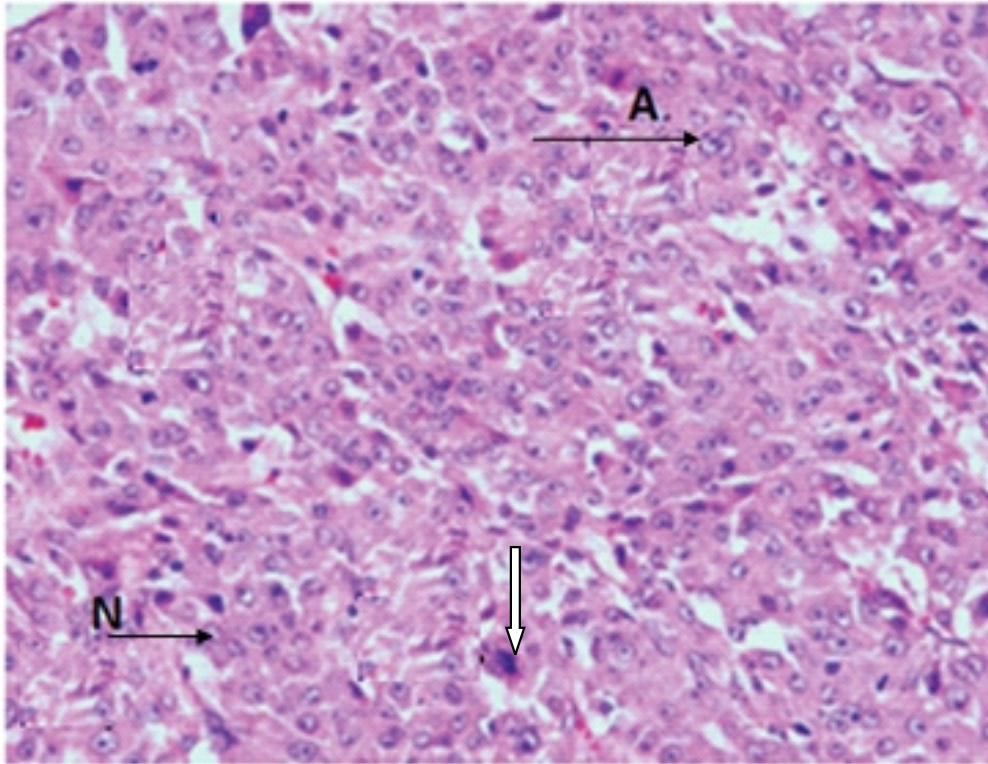
**Table 2: Showing the mean age by gender distribution of subjects with HCC**

<b>Gender</b>	<b>N</b> <b>(%)</b>	Mean ± SD Age (years)
Females	63(41.7)	41.66 ± 20.37
Males	88(58.3)	36.86 ± 14.88

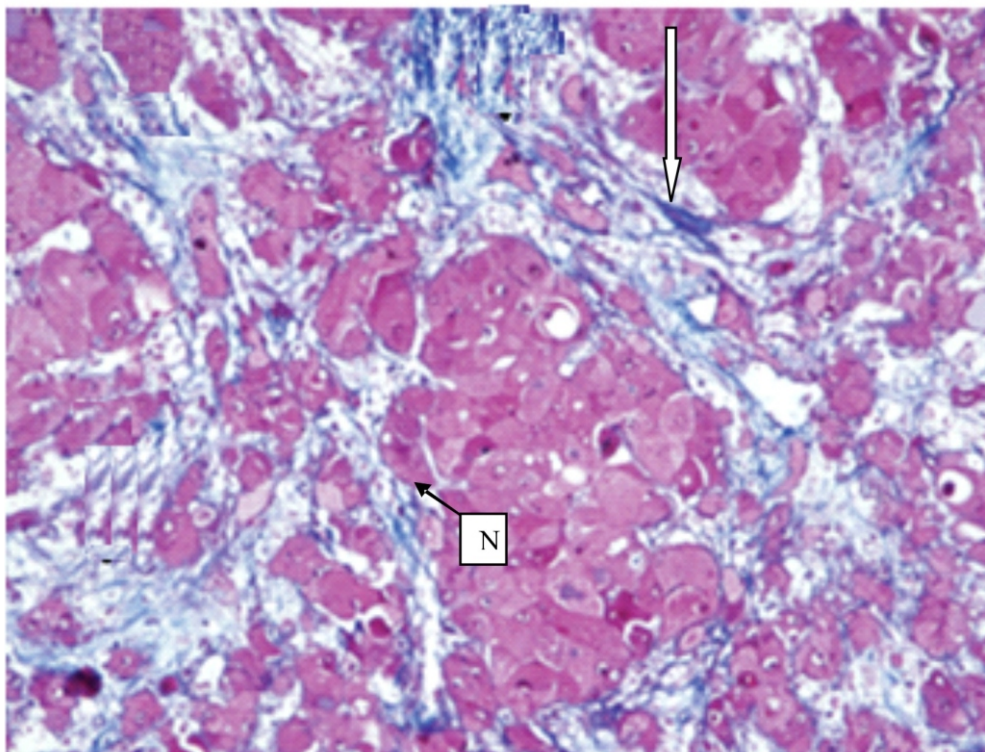
F = 11.007, t = 1.598, p = 0.113, N = number of subjects



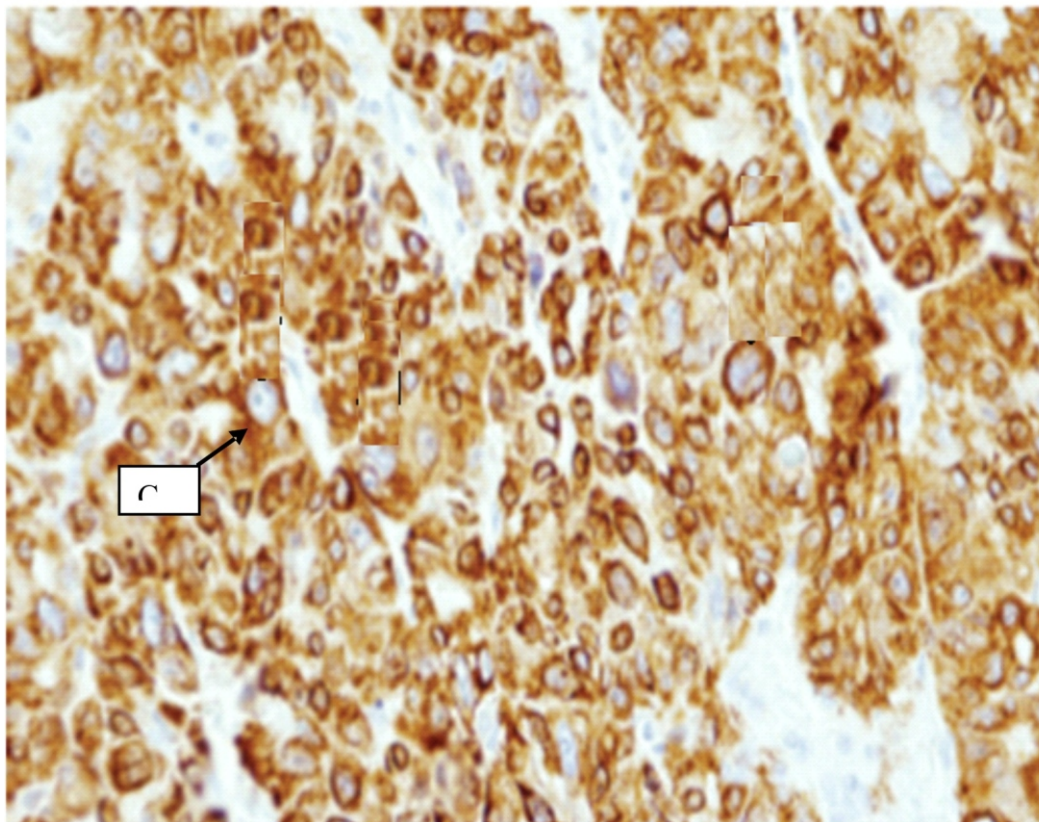
**Plate 1:** Photomicrograph of normal liver (negative control) showing normal arrangement of the central vein (a), portal triad (b) and hepatocytes (c). (H& E stain x 200).



**Plate II:** Photomicrograph of HCC showing nests (N) and trabeculae of neoplastic cells having large nuclei with prominent nucleoli (A). Numerous mitotic figures including atypical forms are noted (white arrow). (H & E stain  $\times 200$ ).



**Plate III:** Photomicrograph of HCC showing nests (N) of neoplastic cells delineated by fibrous bands (white arrow). (Masson's trichrome stain  $\times 200$ )



**Plate IV:** Immunohistochemical stain with cytokeratin showing strong staining by the neoplastic cells.(CK7  $\times$  200).

### Discussion

The prevalence of HCC has been said to be on the increase with underlying predisposing risk factors such as viral hepatitis and Aflatoxin infection (EL-zayadi *et al.*, 2005). It is seen at present too as the principal cause of death among cirrhotic patients (Sangiovanni *et al.*, 2004). Increasing Westernization and adoption of indolent lifestyle may thus pose another danger of increased incidence of HCC in our environment (Abdulkareem *et al.*, 2006). Recent studies have revealed HCC incidence predominantly in the age group 40-50 years (Yuen *et al.*, 2009; Ndubaba *et al.*, 2001). This might be attributed to the various etiologic factors for HCC, the most important of which is chronic infection with HBV. The seroprevalence of HBsAg in Nigeria for example, ranges from 10-40% and that of HCV from 4.5-5% (Omolade *et al.*, 2012). These infection rates range from 49% (Gombe), 54.7% (Ekiti), 61% (Ife), 61.5% (Enugu), 67% (Maiduguri) to 86.5% (Kano) (Laraba *et al.*, 2010; Akande *et al.*, 2009). The mean age of patients with HCC in this

study was  $40.87 \pm 3.25$  years with highest peak in the age group of 30-50 years. This is comparable to the studies carried in Port Harcourt and Benin City, Southern Nigeria and in Maiduguri, Northern Nigeria (Ugiagbe and Udoh, 2013; Mustapha *et al.*, 2007; Seleye-Fubara and Jebbin, 2007) where the mean age of patients with HCC reported was 42 years, 48 years and 38 years, respectively. In Ile-Ife, South Western Nigeria, the peak age group was said to be 40-59 years (Ndububa *et al.*, 2001) with notable predisposing aetiologic factors such as underlying chronic liver disease, scarification marks and use of unorthodox herbal prescriptions. Consequently, effective public awareness on route of transmission of HBV and HCV, general health/social education, food perseveration methods and some socio-cultural practices need to be emphasized.

Microscopically, the tumours observed in this study, varies from well-differentiated to highly anaplastic undifferentiated lesions as similarly reported (Vhritherhire *et al.*, 2016; Seleye-Fubara

and Jebbin, 2007). In well-differentiated and moderately differentiated tumours which were mostly seen in this study, cells that are recognizable as hepatocytic in origin are disposed either in a trabecular pattern recapitulating liver cell plates or in an acinar, pseudoglandular pattern. While in poorly differentiated forms seen, tumour cells can take on a pleomorphic appearance with numerous anaplastic giant cells or be completely undifferentiated and may even resemble a spindle cell sarcoma (Kumar *et al.*, 2005). Fibrolamellar carcinoma although not seen in this study is a distinct variant of HCC that constitutes 5% of HCC cases and occurs in young adults aged 20 to 40 years with equal male and female gender incidence. Morphologically, it is often a single large, hard “scirrhus” tumor with fibrous bands coursing through it and is composed of well-differentiated polygonal cells growing in nests or cords, separated by parallel lamellae of dense collagen bundles (Kumar *et al.*, 2005). Cytologically, tumoral hepatocytes are polygonal, displaying an eosinophilic granular cytoplasm, rounded nuclei and prominent nucleoli. The importance of cell pleomorphism varies according to the degree of differentiation. Immunohistochemical study may be used in routine practice for the diagnosis of HCC where available. Immunophenotypical markers of HCC, include highly specific markers like HepPar1, albumin, fibrinogen,  $\alpha$ 1-anti-trypsin and Alfa-Fetoprotein (Xiao *et al.*, 2006; Kumar *et al.*, 2005). Also using microarray technology, it has recently been shown that a subset of adult HCC displays phenotypical traits of progenitor cells. These tumours retain stem cell markers and express Cytokeratin (CK) 7 and CK19 and usually have poor survival prognosis (Xiao *et al.*, 2006). This is particularly seen in several cases in our study that express cytokeratin 7.

Management option of HCC and diagnosis are dependent on various factors but particularly on tumour size and stage. Tumor grade is also significant. High grade tumour will have poor diagnosis, whereas low grade tumours may go unobserved for many years, as is the case in many other organs.

## Conclusion and Recommendation

HCC is very common in our environment, with early and middle-aged groups as the most vulnerable, and ignorance, poor life style and surveillance as the bane underlying the late presentations and poor prognosis often. Yet, it is undisputed that as rampant and devastating as HCC is, increased survival rate even in cases with badly presenting underlying chronic liver disease is possible with improved surveillance methods (Sangiovanni *et al.*, 2004). Careful health education to improve public awareness and help reduce the burden of HCC in our environment is therefore indispensable in its management, and thus highly recommended.

## Conflict of Interest

We declare that there is no conflict of interest in this study.

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**Citation:** Mairiga, A.A., Adoke, K.U., Zakariya, A.G., Ogefere, H.O., Ataman, J.E. Cytoarchitectural Pattern of Hepatocellular Carcinoma (HCC) in Ahmadu Bello University Teaching Hospital Zaria, Nigeria. *Sokoto Journal of Medical Laboratory Science*; 3(1): 10 - 18

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