HISTOPATHOLOGICAL PATTERN OF LIVER BIOPIES IN ZARIA; A TEN YEAR RETROSPECTIVE ANALYSIS [2004-2013]

BEING A
DISSETRATION FOR THE PART TWO (FINAL) IN PARTIAL FULFILMENT OF THE REQUIREMENT FOR THE FELLOWSHIP OF THE NATIONAL POSTGRADUATE MEDICAL COLLEGE OF NIGERIA IN PATHOLOGY

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DECLARATION

I hereby declare that this Dissertation titled: **HISTOPATHOLOGICAL PATTERN OF LIVER BIOPIES IN ZARIA, A TEN YEAR RETROSPECTIVE ANALYSIS**, is an original study developed by me. It has not been presented to any college for fellowship neither has it been submitted elsewhere for publication.

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DEDICATION

I dedicate this work to my parents, my mother Hajiya Fatima Usman and my late father Alhaji Usman Umar.
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SUMMARY

Introduction: Liver diseases account for a significant number of morbidity and mortality worldwide. Liver biopsy and accurate histologic interpretation of the reports is an important aspect of management of patients with chronic liver diseases.

Objective: The objective of this study was to document the histopathological patterns of liver biopsies in Ahmadu Bello University Teaching Hospital, Zaria over a ten-year period (2004-2013) and to review all cases of chronic viral hepatitis using Ishaq modified histologic activity index (HAI).

Materials and methods: Formalin fixed paraffin embedded tissue blocks and haematoxylin and eosin stained slides were studied. Special stains such as reticulin, perls, masson trichome and PAS were also used in further characterization of specific liver pathology. The biodata and clinical history of cases were extracted from accompanying case cards and departmental records.

Result: The samples of 197 males and 104 females (M: F; 1.9:1) were studied. The age range was 2months to 80years with an overall peak age incidence in the 3rd decade of life. The liver diseases were categorized into congenital (2.3%), infectious conditions (2.9%), hepatitis (56.5%), cirrhosis (15.3%) and neoplastic diseases (18.9%). Overall, Hepatitis was the commonest pathology with 56.5% cases while cirrhosis and hepatocellular carcinoma accounted for 15.3% and 13.6% respectively. Chronic viral hepatitis cases had a male: female ratio of 2.5:1.0 and 42.2% of the cases were mild grade disease while over 70% were stage 0-2 disease using Ishaq histologic activity index. Hepatocellular carcinoma showed a slight male preponderance with peak age distribution in the 4th decade of life and 46.3% of the cases were post-cirrhotic. Hepatotrophic viruses accounted for the bulk of aetiological factors
with hepatitis B virus (HBV) infection recorded in 41.3% of the cases, hepatitis C virus (HCV) in 8.7% and HBV/HCV co-infection in 4.4% cases. Only 6.5% cirrhotic cases were associated with significant alcohol consumption while 32.6% were cryptogenic with no identifiable aetiologic agent clinico-pathologically.

**Conclusions:** The most common liver diseases in Zaria are hepatitis, cirrhosis and hepatocellular carcinoma. All showed a slight male preponderance with peak age of affectation in the third decade of life. Hepatotropic viruses, hepatitis B virus (HBV) and hepatitis C virus (HCV) were the main implicated aetiologic factors in majority of our cases while mild grade disease of chronic viral hepatitis accounted for bulk of the cases reviewed.
CHAPTER ONE

INTRODUCTION

The liver is the largest solid organ in the body with functions ranging from metabolism of fat, synthesis of proteins, storage of glycogen, vitamins and iron to the detoxification of waste products, toxins, drugs and secretion of bile.\(^1\) Thus, the liver is vulnerable to a wide variety of metabolic, toxic, microbial, circulatory, and neoplastic insults.\(^2\) However due to its enormous functional reserve, mild to moderate damages and disease processes are clinically silent and therefore most patients will not require medical intervention until there is significant liver function compromise.

Globally, liver biopsy plays an integral part in the diagnosis, therapy selection, and disease outcome in the management of liver diseases.\(^3\) The procedure is useful in patients with no evidence of hepatic dysfunction and results have been shown to correlate well with findings of liver function tests and even postmortem findings.\(^4\)

Liver diseases account for a significant number of morbidity and mortality worldwide. It is the 8th commonest cause of death\(^5\) with an annual incidence of 72/100,000 population for newly diagnosed cases and an annual mortality of 27,000 in the United States.\(^2\) It is a major burden in sub-Saharan Africa with high mortality rates.\(^6\) Reports from various studies have shown that infective agents particularly viruses account for the bulk of liver diseases in sub-Saharan Africa.\(^6,7\) The major primary diseases of the liver in adults are hepatitis from a variety of processes, alcoholic and nonalcoholic liver disease, cirrhosis and hepatocellular carcinoma (HCC). Hepatic damage also occurs secondary to diseases such as cardiac decompensation, extra hepatic infections and disseminated cancer.\(^2\) Other less commonly encountered diseases are autoimmune hepatitis, primary biliary cirrhosis and primary
sclerosing cholangitis. While in children, biliary atresia, neonatal hepatitis and liver cirrhosis are commonly seen.

Chronic liver disease secondary to hepatotrophic viral infections is a major public health problem globally and sub Saharan Africa has the highest disease burden. Other high prevalence regions of chronic viral hepatitis are Eastern Mediterranean and Western Pacific. The sero-prevalence of HBsAg in Nigeria ranges from 10% to 40% and that of HCV from 4.5% to 5%. In Nigeria, the pattern of liver diseases vary widely for different geographical regions. Studies from Kano and Zaria (north west) Maiduguri (northeast), Jos (north central) and Benin (south south) reported rates ranging from 40.5% to 63.8% for chronic hepatitis and a study from Lagos (southwest) documented the lowest rate of 17.7%. The reported frequencies for liver cirrhosis are 6.3% and 41.1% from studies in Benin and Ile-Ife in southwestern Nigeria respectively, while hepatocellular carcinoma, a malignant liver disease with devastating morbidity and high mortality had frequencies ranging from 12.5% to 39.7%.

In view of the high and varied prevalence rates for the various liver diseases, this study seeks to document the pattern of liver diseases diagnosed from biopsy specimens submitted to the Department of Pathology, Ahmadu Bello University Teaching Hospital (ABUTH) Zaria over a ten year period from January 2004 to December 2013.
JUSTIFICATION FOR THE STUDY

This is the first comprehensive histopathological analysis of liver diseases diagnosed by liver biopsy in the Department of Pathology, Ahmadu Bello University Teaching Hospital (ABUTH) Zaria. The results obtained may identify preventable aetiological and risk factors and will also be a documentation of data for our center as well as reference for further research in the study of the liver.
CHAPTER TWO

AIM

To determine the histopathological patterns of liver diseases diagnosed from liver biopsies submitted to the Department of Pathology, Ahmadu Bello University Teaching Hospital (ABUTH) Zaria and to review all cases of chronic viral hepatitis using Ishaq modified HAI.

OBJECTIVES

1. To determine the frequency, age and sex distribution of liver diseases in Zaria
2. To determine the aetiological factors for liver diseases in Zaria
3. To determine the commonest histologic type of liver disease
4. To compare the findings with similar studies elsewhere locally and international
5. To grade and stage all cases of chronic viral hepatitis using Ishaq modified HAI
CHAPTER THREE
LITERATURE REVIEW

EPIDEMIOLOGY OF LIVER PATHOLOGY

There is significant geographic and regional variability in the incidence and prevalence of liver pathologies the world over. These variability is best understood with the distribution of two main liver pathologies of cirrhosis and hepatocellular carcinoma both of which represent end stage liver diseases and thus indicative of the attendant morbidity and mortality.\textsuperscript{21} Viral hepatitis contributes significantly to the burden of liver diseases and over 2 billion living people have been infected with hepatitis B virus (HBV) while over 350 million of them are chronically infected carriers with no significant liver disease. Majority of these infected carriers will progress to chronic hepatitis, cirrhosis and hepatocellular carcinoma (HCC) thus representing a significant public health burden.\textsuperscript{22} The carrier rate of hepatitis B surface antigen (HBsAg) varies worldwide from 0.1 to 0.2% in Britain, the USA and Scandinavia to 3% in Greece and southern Italy. The rate in Africa and Far East ranges from 10% to 15%. Higher rates are also documented in isolated communities of Alaskan Eskimos (45%) and Australian Aborigines (85%).\textsuperscript{22} The sero-prevalence of hepatitis B surface antigen (HBsAg) in Nigeria ranges from 10% to 40% and that of Hepatitis C virus antibody (HCVab) was 4.5% to 5%.\textsuperscript{13} The World Health Organization (WHO) estimated 170 million chronically infected individuals with HCV globally and 75% of them will develop chronic liver disease while a 2005 health survey report showed chronic HCV infection as the leading indication for liver transplantation in the United States.\textsuperscript{23, 24} Of the HCV-infected patients who develop chronic liver disease, 1.6% will progress to HCC. A more recent survey reported that 1.8% (3.9 million) of the US population was infected with HCV and 74% (2.7 million) of this group had chronic infection associated with HCV viraemia.\textsuperscript{24} Comparatively, the HCV prevalence in
the general Italian population was 5.2% and this value ranged from 2.4% to 3.3% in the northern regions to much higher values in central and southern Italy. However, Africa has the highest WHO estimated regional HCV prevalence of 5.3% with Egypt having the highest prevalence of 17.5% in the world.

The global burden of disease study in 2010 revealed that 800,000-1 million deaths were attributable to liver cirrhosis annually worldwide. One percent of all deaths of people aged 25 years and above in England and Wales were attributed to chronic liver disease and cirrhosis, and it is the twelfth most common cause of death in the United States. Overall, 57% of all cirrhosis were attributable to either HBV (30%) or HCV (27%) infection with resultant mortality of 446,000. Other causes of cirrhosis are alcohol abuse, non-alcoholic steatohepatitis (NASH), biliary disease and iron overload.

Alcohol-related liver disease (ALD) is a significant burden on health with an estimated 4% rate and accounts for an estimated 3.8% of global mortality. In 2010, alcohol-attributable liver cirrhosis accounted for 493,300 deaths representing 0.9% (0.7% for women and 1.2% for men) of all deaths and 47.9% of all liver cirrhosis deaths; an increase from the 4% reported in 1997. Alcohol-attributable liver cancer is responsible for 80,600 deaths worldwide. Alcohol is the leading cause of liver cirrhosis in the developed industrialized countries where alcoholic liver disease (ALD) has a prevalence rate of 11.2% in Italy alone. The prevalence of ALD is low in Africa and other developing nations where infections particularly hepatitis viruses predominates. In Nigeria, a prevalence rate of 4.14% and 5% in Ile Ife and Benin respectively were reported while in Jos, alcohol was found to be the cause of liver cirrhosis in 80% of the patients studied. This high percentage was attributed to local and cultural factors.
Also, non-alcoholic fatty liver disease (NAFLD) has reached epidemic proportions and is currently the most common cause of chronic liver disease in clinical practice.\textsuperscript{32} It is now the commonest liver disorder in the United States and other industrialized countries affecting up to 30\% of the general adult population and 90\% of those with morbid obesity (body mass index >40 kg/m\textsuperscript{2}).\textsuperscript{33} There is an increasing incidence of NAFLD in developing nations due to westernization. Onyekwere et al reported a prevalence rate of 8.7\% in Lagos, Nigeria an urbanized industrialized city.\textsuperscript{34}

Hepatocellular carcinoma (HCC) is the fifth most frequently diagnosed cancer worldwide and the third leading cause of cancer death.\textsuperscript{35} In 2008, an estimated 748,300 new liver cancer cases and 695,900 liver cancer deaths were reported reflecting the poor prognosis of this disease.\textsuperscript{36} It is also responsible for 47,000 deaths annually in Europe.\textsuperscript{21} There is substantial variation in the distribution of liver cancer incidence and mortality across geographical locations. HCC is more common in regions of Africa and Asia than in Western countries and more common in middle and low income countries than in developed nations.\textsuperscript{36} In 2000, HCC was most prevalent in eastern Asia with approximately half of all cases occurring in China alone.\textsuperscript{36, 37} The estimated age-adjusted incidence rate (AAIR) per 100,000 men was approximately 10 times higher in eastern Asia compared to Australia and New Zealand, with Eastern Asia and central Africa having AAIR rates of 36.9 per 100,000 males in and 13.4 per 100,000 females respectively compared with low rates of 3.4 per 100,000 males and 1.7 per 100,000 females in Northern Europe. Lowest AAIRs of 1.3 per 100,000 were recorded in New Zealand.\textsuperscript{37}

Geographic variation in the epidemiology of HCC can also be observed across a region. A good example is a report from Latin America,\textsuperscript{41} In Brazil, HCV infection leading to HCC is more commonly associated with the southern states and the cities of Sa˜o Paulo and Rio de
Janeiro, whereas HBV infection occurs more frequently in the northern states. HCC is also becoming an increasingly frequent cancer in Mexico with a 5% increase per year in referrals and the majority of patients present with cirrhosis (72.3%) and HCV infection as common factors in 44.7% cases. On the other hand, HBV infection has a prevalence of 8.4% only because it is not an endemic problem in Mexico. This is clearly in contrast to other areas where HBV infection accounts for 70%–80% of HCC cases worldwide. In Argentina, the increase in HCC incidence has been linked to HCV infection though alcoholic cirrhosis remains the primary cause of HCC while HBV infection is the third cause in this area. However, in areas such as Venezuela and Peru, HBV infection is considered to be the primary driver of HCC. On the other hand, HBV infection has a prevalence of 8.4% only because it is not an endemic problem in Mexico. This is clearly in contrast to other areas where HBV infection accounts for 70%–80% of HCC cases worldwide. In Argentina, the HCC incidence has been linked to HCV infection though alcoholic cirrhosis remains the primary cause of HCC while HBV infection is the third cause in this area. However, in areas such as Venezuela and Peru, HBV infection is considered to be the primary driver of HCC. A study from Saudi Arabia reported that 46% and 62% of patients with HCC were associated with HCV and HBV respectively.

Diseases of the liver are one of the most significant causes of morbidity and mortality in children. Epidemiologically, the patterns of hepatic disorders in this age group differ greatly from adults. Biliary atresia and neonatal hepatitis predominates. Other documented diseases are secondary haemochromatosis, storage disorders, fatty liver and cirrhosis. Cryptogenic liver cirrhosis (26%), neonatal hepatitis (20%), and fatty liver (12%), were reported to be the most common histological diagnosis of liver biopsy in Sudan Northeastern Africa. In 1991, Obafunwa et al in their study of childhood liver diseases in Jos, Nigeria reported hepatic schistosomiasis as the most common liver disease in Nigerian children followed by cirrhosis in 25% and biliary atresia in 4.2%. NAFLD is also a leading cause of CLD in children and its increasing prevalence can be predicted by obesity and the male sex. Progression to fibrosis, cirrhosis and HCC in this group is well documented. Neoplastic diseases of the liver are not uncommon and include hepatoblastoma and HCC.
Generally liver diseases are commoner in males than females with a male to female ratio of 5.1:1 for HCC, 2.5:1 for cirrhosis and 1.2:1 for non alcoholic fatty liver. Chronic hepatitis B infection is predominantly in males.\textsuperscript{22}

**THE LIVER BIOPSY AND INDICATION**

The liver biopsy for diagnostic purposes was popularised by Menghini in 1958 though the first biopsy procedure was credited to Paul Ehrlrich in 1883.\textsuperscript{46} Subsequently, it has become central to the management of hepatic diseases despite being an invasive procedure and is widely used in clinical practice as the gold standard in assessing the nature and severity of liver diseases.\textsuperscript{47-551} The size of the biopsy specimen varies between 1 to 3 cm in length and between 1.2 to 2 mm in diameter and represents 1/50,000 of the total mass of the liver.\textsuperscript{52} Usually for the evaluation of diffuse liver disease a specimen of 1.5-2.5 cm in length is adequate for a diagnosis though optimal length is 2.5 cm.\textsuperscript{53} The number of portal triads present in the specimen is also important and should contain at least six to eight portal triads.\textsuperscript{54} In cases of chronic liver disease in which the extent of injury may vary among portal triads, 11 complete portal tracts are recommended.\textsuperscript{50} Cholongitas et al and Bravo AA, amongst others outlined the indications for liver biopsy and these include:

- Grading and staging of chronic hepatitis B and C.
- Evaluation of abnormal results of biochemical tests of the liver in association with a serologic work up that is negative or inconclusive.
- Evaluation of fever of unknown origin, with a culture of tissue.
- Diagnosis, grading, and staging of non-alcoholic steatohepatitis, alcoholic liver disease or autoimmune hepatitis.
- Diagnosis of hemochromatosis in index patient and relatives, with quantitative estimation of iron levels.
- Diagnosis of Wilson’s disease with quantitative estimation of copper levels.
- Evaluation of cholestatic liver diseases, primary biliary cirrhosis and primary sclerosing cholangitis.
- Evaluation of the efficacy or the adverse effects of treatment regimens (e.g., methotrexate).
- Therapy for psoriasis and effectiveness for therapies for chronic viral hepatitis.
- Diagnosis of a liver mass or intrahepatic neoplasm.
- Evaluation of the status of the liver post transplantation or of the donor liver before transplantation.
- Diagnosis and evaluation of systemic disorders such as sarcoidosis, lymphoma, acquired immunodeficiency syndrome and amyloidosis.
- Evaluation of unexplained jaundice, acute hepatitis of uncertain cause and hepatomegally.

Similarly, liver biopsy is used in securing the initial diagnosis of autoimmune diseases (autoimmune hepatitis), primary sclerosing cholangitis (PSC) and primary biliary cirrhosis (PBC).\textsuperscript{55}

Currently, several techniques available for obtaining the liver tissue include percutaneous, transjugular, laproscopic, fine needle aspiration under ultrasonography or computed tomography and perioperatively. Each of these techniques has its own merits and demerits. The decision to select a particular technique is based upon available expertise and the particular clinical situation.\textsuperscript{52}

There are three general categories of needles used to obtain a percutaneous liver biopsy, suction needles (Menghini needle, Sure-Cut; a modified Menghini needle, Klatskin needle,
Jamshidi needle), the cutting needles (Trucut needle, Vim-Silverman needle) and the Spring loaded cutting needles that have a triggering mechanism. The two main types of needle currently being used are the Trucut and the Menghini needles and both use different methods for sampling hepatic tissue. The former is cutting and resultant specimens are larger and give more information about liver architecture thus increasing the diagnostic yield. If cirrhosis is clinically suspected, a cutting needle is preferred over a suction-type needle, as fibrotic tissue tends to be fragmented with the suction type needle. 56, 57

**HISTOLOGICAL GRADING AND STAGING OF CHRONIC HEPATITIS**

The liver biopsy examination/evaluations were designed primarily as a diagnostic aid in determining the aetiology of liver dysfunctions. While some liver diseases such as focal nodular hyperplasia, hepatic adenoma, HCC and hepatic schistosomiasis have specific diagnostic features, many others such as HBV and HCV infection, alcoholic related liver diseases, non-alcoholic steatohepatitis, primary biliary cirrhosis and autoimmune hepatitis exhibit diffuse parenchymal damage requiring a systematic assessment of disease extent and outcome. 58

The diagnostic criteria morphologically describe:

- Necroinflammatory activity: This indicates disease activity, severity and response to therapy and is used for grading.
- Fibrosis: Indicates disease prognosis in the long term and is used for staging.
- Degenerative alteration of hepatocytes
- Biopsy point rating

**Grading:** This is based on a 4 point scale assessing the intensity of inflammatory and necrotic processes.
- Piecemeal necrosis including bridging necrosis: a specific morphological change due to cytotoxic reaction of lymphocytes to hepatocytes. Leading to the death of hepatocytes at the margin of the lobule and the destruction of the limiting plate. The process extends piecemeal towards the centre of the lobule.

- Focal lobular necrosis: The severity of lobular necrosis may encompass changes from a single focus of lymphocytic or lymphocytic-granulocytic infiltration without hepatocyte death, to inflammatory-cell infiltration with single hepatocyte destruction.

- Advanced confluent bridging necrosis involving a considerable portion of lobular surface with the associated collapse of the lobular stroma or perivenular confluent necrosis. Additional morphological features include ballooning degeneration, steatosis, cholestasis and bilirubinostasis.

- Portal inflammation: The assessment of inflammatory infiltrates in the portal spaces is of less prognostic significance due to difficulties in objective assessment. Thus it was inappropriate for clinical evaluation since it is a defining lesion for chronic hepatitis. Also prominent lymphoid aggregates or follicles of HCV may falsely increase the severity of necro inflammatory activity compared to lesions where such lymphoid aggregates are atypical.

**Staging:** This is based on a 4 point scale proposed by Batts and Ludwig and can be accurately assessed after additional histochemical staining techniques such as Masson’s trichome for the detection of collagen fibres and their location should be determined to assess its severity.

Stage 1- Portal fibrosis: only the portal tracts alone are involved in fibrosis.
Stage 2- Periportal fibrosis: presence of collagen fibres in portal tracts with extension into the lobule or formation of single fibrous bridge that connect adjacent portal tracts i.e. porto-portal fibrosis.

Stage 3- Bridging fibrosis: fibrous bridges connecting adjacent portal tracts or portal tracts and central venule with architectural distortions.

Stage 4-Nodular regeneration

**Biopsy:** point rating is useful in statistical evaluation of process activity and involves a detailed description of the specimen for proper interpretation by the clinician.

The last point of this protocol is to establish diagnosis encompassing disease grade and stage. Grading and staging is done for biopsy specimen which fulfil these laid down criteria.

Diagnostic aids are:

- Lobular inflammatory cells infiltration – Active hepatitis
- Portal and periportal inflammation – chronic hepatitis
- Plasma and lymphocytic infiltrates and bile ducts destruction – autoimmune hepatitis
- Lymphocytic aggregates/follicles – seen in some forms of Chronic HCV infection
- Portal hepatitis without periportal or lobular infiltration – Non active hepatitis
- Mild inflammation of portal tract – portal hepatitis
- Periportal hepatitis with focal hepatocytes destruction – piecemeal necrosis
- Piecemeal necrosis or marked lobular necrosis with inflammatory cells infiltration – chronic hepatitis.
- Marked fibrosis either septal or cirrhotic – chronic hepatitis or chronic biliary disease.
LITERATURE REVIEW OF VARIOUS GRADING AND SCORING SYSTEMS

The first published qualitative classification of chronic hepatitis by an international group was in 1968 and was revised in 1977. This group codified terminologies such as chronic persistent hepatitis, chronic lobular hepatitis and chronic active hepatitis based on the degree of disease activity and to provide prognostic information and criteria for the use of immunosuppressive therapy. Prior to this period most hepatological examination was descriptive and subjective thus leading to interpretation discrepancies among clinicians.

The objective histological activity index established in 1981 by Knodell et al has undergone different modifications and scoring systems by Ishak, Scheuer, Batts-Ludwick and Metavir in order to ascertain the natural history, pathogenesis, serological features and appropriate therapy for chronic hepatitis. This objectively enabled statistical analysis of research result. However, in 1984 new diagnostic criteria for chronic liver diseases was introduced by the World Congress of Gastroenterology and International Association for the Study of the Liver (IASL). This has since been adopted and updated by the International Working Party in 1994. The various classification systems used in scoring and gradings are outlined below:

**The Old Qualitative Classification:** This was proposed by an international group in 1968 and subsequently revised in 1977 by Bianchi et al. It is essentially a measure of necroinflammatory activity and it does not recognize the fibrosis stage and aetiology. This classification was declared obsolete by the International Working Party, which convened at the recommendation of the World Congress of Gastroenterology in 1994, because it is not a good indicator of prognosis.

**Knodell (1981) Histological Activity Index (Appendix II):** This was the first system of semiquantitative assessment of chronic hepatitis and is widely regarded as the benchmark for objective, semiquantitative, reproducible description of the various morphological lesions of chronic hepatitis. It provides a systematic methodology and terminology to replace or
supplement the Old Qualitative Classification, and also develop a means of evaluating serial biopsies in asymptomatic patients for tracking disease progression or the response to therapeutic intervention. This system however, does not separate grading from staging and scores are not sequential (appendix ii).

**Scheuer (1991) Simplified System for Scoring Chronic Viral Hepatitis (Appendix III):**
This is a simplified system that assessed two main components of necroinflammatory activity and fibrosis separately using on a scale of 0–4. The necroinflammatory activity is further scored based on lobular and portal-periportal activities. The advantage of this system is the separation of this distinct processes.

**Ishak (1994) Histological Grading and Staging of Chronic Hepatitis (Appendix IV):**
This is also called the Ishaq Modified Histological Activity Index. The system is an extension and modifications of the original Knodell HAI whereby a continuous scale is used for assessing and scoring each of the features of necroinflammatory activity and fibrosis. In assessing necroinflammatory activity, confluent necrosis is separated from periportal hepatitis and is considered as a separate activity. The combination of scores for each of the four individual necroinflammatory categories and histological grading, scores ranging from 0–18 is used in grading while fibrosis is staged separately on a scale of 0–6. This detailed system measures disease progression from no fibrosis to bridging fibrosis and eventually established cirrhosis.

**Batts-Ludwig (1995) System (Appendix V):** This simple system also grades necroinflammatory activity and stages fibrosis separately. Three components of necroinflammatory activity are scores on a scale of 0-4 to get a maximum score of 12 based on the degree of interface hepatitis, parenchymal injury and inflammation. This system is similar to Scheuer because fibrosis is considered separately on a continuous scale of 0-4.
Metavir group system (Appendix VI): This system was developed by establishing criteria to be assessed by a panel of Pathologists. The microscopic descriptions were subsequently analysed to identify the most consistently reproducible scoring method. This approach is different from the other systems because it is relatively simple and uses scores of mild, moderate or severe for activity and four fibrous stages of disease progression.65

LITERATURE REVIEW OF SELECTED LIVER PATHOLOGIES

HEPATITIS B VIRAL HEPATITIS

Over 300 million people suffer from chronic infection with Hepatitis B virus (HBV), a member of the hepatotrophic DNA viral family of hepadnaviruses. Its mode of transmission varies with geographical areas. In high prevalence regions of the world, perinatal transmission during childbirth accounts for 90% of cases, while in intermediate prevalence areas, horizontal transmission through minor cuts, breaks in skin and mucous membrane especially in early childhood is the dominant mode. In low prevalence areas such as the United States, unprotected heterosexual or homosexual intercourse and intravenous drug abuse are the chief modes of spread.66 The incidence of transfusion-related spread has dwindled greatly in recent years due to the screening of donated blood for HBsAg and the exclusion of paid blood donors.2, 67

The HBV hepatitis is highly endemic in Africa with prevalence of about 8%.66 The seroprevalence of HBsAg in Nigeria ranges from 10% to 40% and that of HCV from 4.5% to 5%.13 In 2014, Mbaawuaga et al reported a 12.0% seroprevalence of HBsAg in 1535 randomly collected blood specimens from different groups of consenting subjects in Benue State, Nigeria.68 Musa et al studied 46 published articles in a recent 13 years systematic review and meta analysis of the prevalence of HBV infections in Nigeria and reported a range of 0.5% to 46.8% and a pooled prevalence of 13.6% among Nigerians.69

The hepatitis B virus has sometimes been called ‘the silent killer’ because infected adults often remain undiagnosed and thus untreated until it is too late. HBV produces a spectrum of diseases ranging from acute hepatitis with recovery and clearance of the virus,
nonprogressive chronic hepatitis, progressive chronic disease ending in cirrhosis, fulminant hepatitis with massive liver necrosis to an asymptomatic carrier state. HBV-induced chronic liver disease is an important precursor for the development of hepatocellular carcinoma.\textsuperscript{67} The natural history of chronic HBV infection is complex and associated with geographical and age related differences. It is predominant in males and infected individuals aged over 40 years have poorer prognoses. Most people infected at birth are asymptomatic during their first 20-30 years; this is the immune tolerant phase which later breaks down and results in alanine transaminase (ALT) flares-up due to activation of the immune response against HBV. After an ALT flare, 80-90\% of chronically infected patients experience a great reduction of HBV replication; these patients seroconvert, from HBeAg to anti-HBe antibody and become inactive carriers. In the remaining 10-20\% of chronically infected patients, ALT remains elevated and active HBV replication persists, resulting in disease progression to chronic hepatitis, liver cirrhosis and hepatocellular carcinoma.\textsuperscript{66} Although the precise pathogenetic mechanisms differentiating inactive carriers from chronic hepatitis patients are unclear, recent immunological analyses have provided new insights into the understanding of these mechanisms.\textsuperscript{70}

Livers of patients with low HBV replication contain intralobular CD8+ T lymphocytes, suggesting that the host immune system recognizes viral antigens and may carry out immune surveillance in the livers of inactive carriers. These HBV-specific CD8+ T cells effectively control viral replication without damaging infected hepatocytes in inactive carriers, but fails to do so in patients with chronic hepatitis.\textsuperscript{70, 71} Two possible mechanisms have been hypothesized for the failure of viral control. One involves regulatory T cells (Tregs) and the other the co-stimulatory molecule PD-1. Tregs expresses transcription factor Foxp3 that exert negative control on a variety of physiological and pathological immune responses, resulting in maintenance of immunological self-tolerance.\textsuperscript{71} Circulating and intrahepatic Tregs are involved in persistent infection by hepatitis virus. CD4+, CD25+ cells and Foxp3+ cells are increased in the livers of patients with chronic hepatitis B, and patients with high viral load have a higher proportion of Tregs in the liver, suggesting that intrahepatic Tregs suppress antiviral immune responses in the liver.\textsuperscript{71, 72}

PD-1 is a surface receptor critical for the regulation of T cell function and binding to its ligands PD-L1 and PD-L2 results in the antigen-specific inhibition of T-cell proliferation, cytokine production and cytolytic function. In the liver, PD-1 is expressed on lymphocytes while PD-L1 is expressed on lymphocytes, hepatocytes and sinusoidal endothelial cell and PD-L2 is expressed on Kupffer cells and ductular cells. Intrahepatic HBV-specific CD8+ T
cells express higher levels of PD-1 and upregulation of intrahepatic PD-1/PD-L1 is associated with liver inflammation and ALT elevation.\(^7\) Signals from PD-1 inhibit HBV-specific T cells resulting in insufficient antiviral responses and liver inflammation. Importantly, PD-1/PD-L1 blockade increases CD8+ T cell proliferation and enhances IFNγ and IL-2 production by intrahepatic lymphocytes.\(^73-75\) These findings suggest that inhibiting PD-1/PD-L1 may have therapeutic potential for the control of hepatitis B.\(^74\)

The diagnosis of chronic hepatitis is usually by a combination of clinical history, physical examination, relevant biochemical and serological tests and liver biopsy.

**HEPATITIS C VIRAL HEPATITIS**

Choo et al cloned the HCV genome in 1989.\(^24\) It is an RNA virus that infect humans and chimpanzees, causing similar disease in both species. It is a hepatotropic non-cytopathic virus that is very efficient in evading the host immune response.\(^76\)

It is a leading cause of chronic liver disease in the world and four million new infections occur yearly, thus making it a leading public health problem with a prevalence of 5.3% and an estimated 32 million infected people globally.\(^77\) HCV accounts for about 70% cases of chronic hepatitis, 40% of cirrhosis, and 60% of HCC. Chronic infection with hepatitis C virus (HCV) is the predominant aetiology for the development of HCC worldwide and accounted for 15-30% of liver transplantation.\(^77,78\)

Transmission is often parenterally but can also be vertically or sexually. The virus is 4 times more infectious than Human Immunodeficiency Virus (HIV). It also requires less exposure than HIV to cause infection. Direct blood or fluid exposure, through percutaneous or permucosal exposure to infectious blood or bodily fluid is the most apparent and documented mode of HCV transmission.\(^24\) Direct exposure includes transfusion of HCV-contaminated blood products, parenteral drug use, accidental needle injuries in health care workers, and receipt of an organ transplant from an infected donor. The risk of acquiring HCV from sexual activity remains controversial.\(^24,79\)

The rate of chronicity after acute HCV infection is not well established but is believed to exceed 70%.\(^72\) Several factors that correlate with a lower rate of chronicity have been identified, including younger age at infection, female sex, non-black race and the development of jaundice during acute infection. Patients with immunologic deficits are at an increased risk of developing chronic HCV infection.\(^24,77\)
Factors associated with development of advanced liver disease are HCV genotype and serum HCV RNA level, race (black patients are less likely to progress to cirrhosis), coinfection with other viruses such as HBV, HIV and genetic influences. T cells play integral role in the immunopathogenesis of chronic HCV hepatitis. Intrahepatic CD4+ T cells, most of which are Th1 cells producing IFN-γ but not IL-4 and IL-5 are located in portal and periportal areas, with the proportions of these cells correlating with histological activity index. However, no correlation has been found between the proportion of intrahepatic CD4+ T cells and viremia or serum ALT levels. Most intrahepatic CD4+ T cells in the livers of patients with chronic hepatitis C are CD45RO+, but the percentages of CD4+ CD27+ and CD4+ CD28+ T cells are lower, suggesting that memory T cells at relatively early stages of differentiation are involved in liver inflammation.

In patients with chronic hepatitis C, CD8+ T cells are located in the lobules within areas of inflammation and spotty necrosis, with the proportion correlating with histological activity index. Intrahepatic CD8+ T cells show higher percentages of CCR7+L-selectin- cells, which are distinct from central memory and effector memory cells. The CCR7 ligands, CCL19 and CCL21 are expressed on sinusoidal endothelial cells suggesting a mechanism of CD8+ T cell recruitment to the inflamed liver. Other chemokine receptors that mediate T cell recruitment are CCR5 and CXCR3. Similar to intrahepatic T cells in patients with chronic hepatitis B, intrahepatic HCV-specific cells were found to express high levels of PD-1.

**ALCOHOLIC LIVER DISEASE**

The pathology of alcoholic liver disease (ALD) comprises three major lesions and the injury rarely exist in a pure form: (1) fatty liver, (2) alcoholic hepatitis and (3) cirrhosis. Many other types of injury, including perivenular fibrosis, venous occlusive lesions, microscopic cholangitis and chronic active hepatitis may also be seen. The quantity, frequency and pattern of alcohol consumption are all significant determinants of ALD. Fatty liver is present in more than 90% of binge and chronic drinkers. A much smaller percentage of heavy drinkers will progress to alcoholic hepatitis, a precursor to cirrhosis. Women are more susceptible to alcoholic liver injury and develop advanced liver disease with substantially less alcohol intake.

The prevalence of ALD is low in Africa and other developing nations where infections particularly hepatitis viruses predominates. In Nigeria, a prevalence rate of 4.14% and 5% in Ile Ife and Benin respectively were reported while in Jos, alcohol was found to be the cause
of liver cirrhosis in 80% of the patients studied. This high percentage was attributed to local and cultural factors.

The threshold for alcoholic liver disease in men is an intake of more than 60–80 g/d of alcohol for 10 years, while women are at increased risk for developing similar degrees of liver injury by consuming 20–40 g/d. Ingestion of 160 g/d of alcohol is associated with 25–fold increased risk of developing alcoholic cirrhosis. Gender-dependent differences result from alcohol pharmacokinetics and metabolism and the estrogen-dependent response to gut-derived endotoxin (LPS) in the liver. Estrogen increases gut permeability to endotoxins, which in turn, increase the expression of the LPS receptor CD14 in Kupffer cells. This predisposes to increased production of pro-inflammatory cytokines and chemokines. In addition, social, immunologic and heritable factors have all been postulated to play a part in the development of the pathogenic process.

Chronic infection with hepatitis C (HCV) is an important co-morbidity in the progression of alcoholic liver disease to cirrhosis in chronic and excessive drinkers. Even moderate alcohol intake of 20–50 g/d increases the risk of cirrhosis and hepatocellular cancer in HCV-infected individuals. Patients with both alcoholic liver injury and HCV infection develop decompensated liver disease at a younger age and have poorer overall survival. Increased liver iron stores and rarely, porphyria cutanea tarda can occur as a consequence of the overlapping injurious processes secondary to alcohol abuse and HCV infection. In addition, alcohol intake of more than 50 g/d by HCV-infected patients decreases the efficacy of interferon-based antiviral therapy.

Although alcohol is a direct hepatotoxin, only 10% to 20% of alcoholics will develop alcoholic hepatitis. The hepatic metabolism of alcohol initiates a pathogenic process involving production of toxic protein-aldehyde adducts, endotoxins, oxidative stress, immunologic activity and pro-inflammatory cytokines release. The complex interaction of intestinal and hepatic cells is crucial to alcohol-mediated liver injury because tumour necrosis factor (TNF-) and intestine-derived endotoxemia facilitate hepatocyte apoptosis and necrosis. Stellate cell activation and collagen production are key events in hepatic fibrogenesis while the resulting fibrosis determines the architectural derangement of the liver following chronic alcohol ingestion.

Pathologically the liver has a limited repertoire of response to injury and alcoholic fatty liver has traditionally been regarded as entirely benign though similar to the spectrum of nonalcoholic fatty liver disease. Microscopically, steatosis, hepatocytic ballooning, apoptosis,
mixed lobular inflammation, Mallory–Denk bodies (hyaline body), megamitochondria, portal lipogranuloma and the unique pattern of perisinusoidal/pericellular fibrosis are usually seen. Specific features for alcoholic steatohepatitis (ASH) are canalicular cholestasis, cholangiolitis characterised by marked ductular reaction and acute inflammatory infiltrate in the portal regions and lymphocytic phlebitis, obliterative fibrosis of the terminal hepatic venule and the unique lesion of sclerosing hyaline necrosis.2, 67, 81

BILIARY ATRESIA

Biliary atresia is a disorder of infants characterised by the inflammatory and sclerotic obliteration of part or the entire extrahepatic biliary tree with varying involvement of the intrahepatic bile ducts. Biliary atresia being the more common of the structural causes of neonatal cholestatic jaundice is the single most frequent cause of death from liver disease in early childhood and accounts for 50% to 60% of children referred for liver transplantation due to the rapid progression to secondary biliary cirrhosis.2

The incidence of biliary atresia is between 1:8,000 and 1:17,000 live births with an overall female preponderance of up to 1.7:1 in the Western series. The incidence is higher in Japan and China (1 in 9,600) than in Europe and the UK (1 in 16,000).82 In most of Africa including Nigeria, incidence data are not available, though individual institutional reports suggest that up to five children with this disorder are encountered yearly in many centres.11, 83, 84

There are many aetiologic factors that have been proposed, which include genetic factors, congenital developmental anomaly such as failure of recanalisation, antenatal ischaemia, viral and other infectious causes. None of these have been proven and the pathogenesis remains unknown. However, two major forms of biliary atresia are recognized; based on the presumed timing of luminal obliteration. The perinatal form of biliary atresia is commoner and characterized by destruction of a normally developed biliary tree soon after birth. While the foetal form accounts for as many as 20% of cases. It is commonly associated with other anomalies resulting from ineffective establishment of laterality of thoracic and abdominal organ development. The characteristic anomalies are polysplenia, asplenia, situs invertus, absence of inferior vena cava and pre-duodenal portal vein which Sinha C K et al term Biliary Atresia Splenic Malformation (BASM) syndrome. In these infants there is a high incidence of first trimester maternal problems such as diabetes.82, 85

Pathologically, the lumen of the extrahepatic duct is obliterated at variable levels and this forms the basis for the commonest classification in clinical use by the Japanese Association of Pediatric Surgeons (JAPS).84 Type 3 is the commonest accounting for >90% and has the
most proximal level of obstruction in the porta hepatis with no visible duct. In type 2, the atresia extends up to the common bile duct whereas in type 1, atresia extends up to the common hepatic duct level. An important variation is that of cystic change seen in about 5% of cases within some part of the extrahepatic biliary tract. Some cysts contain mucus while others contain bile which may results in diagnostic confusion with a true choledochal cyst. In cystic biliary atresia, the wall is invariably thickened, lacks an epithelial lining and communicates poorly with abnormal non-dilated intrahepatic ducts.\(^8\)

Histologically, there are inflammation and fibrosing stricture of the hepatic or common bile ducts, periductular inflammation of intrahepatic bile ducts and progressive destruction of the intrahepatic biliary tree. Liver biopsy usually reveals marked bile ductular proliferation, portal tract oedema, fibrosis and parenchymal cholestasis. Other features seen in some cases include inflammatory destruction of intrahepatic ducts leading to paucity of bile ducts and absence of oedema or bile ductular proliferation. In uncorrected cases and cases not recognized early, cirrhosis develops within 3 to 6 months of birth.\(^2, 67\)

There have been significant improvements in the prognosis for infants with biliary atresia because of the sequential employment of two major surgical techniques of portoenterostomy and liver transplantation. Kasai’s portoenterostomy procedure have revolutionised the treatment of patient with biliary obstruction that was traditionally considered to have non-correctable biliary atresia. Liver transplantation is the last treatment option for failed kasai operation.\(^82, 85\)

**CIRRHOSIS**

Cirrhosis is the twelfth most common cause of death in the United States and accounts for a significant proportion of liver-related deaths. WHO reports that liver cirrhosis accounted for 1.8% of all deaths in Europe.\(^21\) Cirrhosis of the liver is a major risk factor for the development of HCC and constitutes a major burden of liver morbidity. A recent study from Bangladesh reported 77% of patient with hepatocellular carcinoma suffered from cirrhosis.\(^86\) while Hyasinta J et al from Tanzania reported the presence of cirrhosis coexisting with HCC in 66.2% of their patients.\(^87\)

The prevalence of cirrhosis in Nigeria as in other parts of sub Saharan Africa showed great variability. Studies from Ife, Ibadan and Lagos, all in southwest Nigeria reported rates of 41.4% 18.8%, and 17.7% respectively, though a more recent report from Ibadan by Lawan and Ogunbiyi recorded an increase rate of 23.4%.\(^18, 88, 89\) In Enugu southeast, Nigeria liver cirrhosis was reported as 20.4% of all the liver diseases studied\(^90\) and in Benin South-South,
Nigeria a lower rate of 6.3% was reported by Ugiagbe et al. Adeniji et al reported 13.9% in Ilorin North-Central, Nigeria while in Jos it was 30.8%. In Zaria and Kano North-West, Nigeria rates of 15.8% and 13.5% were reported respectively.

The common aetiologic factors in US, Europe and other developed nations were NAFLD, ALD and HCV infections, while in sub-Saharan Africa and Asia viral aetiology predominated. In most of the reports from Nigeria like other parts of sub-Saharan Africa hepatitis B viral infection is the commonest aetiologic agent incriminated. Other documented aetiologic factors like α1-antitrypsin deficiency, haemochromatosis, autoimmune hepatitis, Wilson’s disease and drug toxicity are less common in developing nations. In children biliary disease with secondary cirrhosis and cryptogenic cirrhosis are common aetiologic factors. Cirrhosis as an end stage liver disease is now controversial because in some setting once the treatment and/or removal of the inciting agent is instituted regression occurs. Successful treatment may involve eradication of a virus (eg, chronic hepatitis C), control of the inflammatory process following inhibition of viral replication (eg, chronic hepatitis B) or suppression of autoimmunity (autoimmune hepatitis) and removal of the offending agent (eg, alcohol, iron). Regression of fibrosis may take place in precirrhotic and cirrhotic livers.

Nonetheless, cirrhosis is defined by three main morphologic characteristics:

- Bridging fibrous septa in the form of delicate bands or broad scars linking portal tracts with one another and portal tracts with terminal hepatic veins. Fibrosis is the key feature of progressive damage to the liver.
- Parenchymal nodules containing hepatocytes encircled by fibrosis, with diameters varying from <0.3 cm, (micronodules) to several centimeters (macronodules). Nodularity results from cycles of hepatocyte regeneration and scarring
- Disruption of the architecture of the entire liver by parenchymal injury and consequent diffuse fibrosis, extending throughout the liver.

Cirrhosis results from interplay between parenchymal damage, inflammation, fibrogenesis and fibrolysis and hepatocellular regeneration. Repetitive liver damage incites an inflammatory response with activation and proliferation of mesenchymal cell populations within the liver which remodel the extracellular matrix by progressive accumulation of scar proteins (fibrosis) that alters organ structure and function thus resulting in cirrhosis and liver failure. These mesenchymal cells (fibroblasts) are derived from sources within and outside the liver and include fibroblasts expressing alpha-smooth muscle actin (myofibroblasts).
which are derived from the transdifferentiation of quiescent hepatic stellate cells and bone marrow in CLD. Fibrogenic fibroblasts may also be generated through liver epithelial mesenchymal transition and is sensitive to the cytokines and chemokines coming from the liver-resident macrophages and infiltrating inflammatory cells. Other cytokine involved in fibrogenesis are transforming growth factor β (TGF-β) and its receptors, metalloproteinase 2 (MMP-2) and tissue inhibitors of metalloproteinases 1 and 2 (TIMP-1 and -2). When converted into myofibroblasts, the cells release chemotactic and vasoactive factors, cytokines, and growth factors.\textsuperscript{2, 67}

Morphologically, cirrhosis is classified based on the size of the nodules. Micronodular if nearly all of the nodules are less than 3 mm in diameter and macronodular if greater than 3 mm in diameter while a mixed micro-macronodular cirrhosis comprises approximately equal numbers of both nodules. The size of the nodule is important in defining the etiology of the process, however this is relative because micronodular cirrhosis may convert into a macronodular type under favorable conditions for parenchymal regeneration.

HEPATOCELLULAR CARCINOMA

Hepatocellular carcinoma (HCC) is a malignant tumour derived from hepatocytes and is a major public health problem worldwide.\textsuperscript{37} It is the commonest primary tumour of the liver and the 5th commonest malignancy worldwide, it is also the third leading cause of cancer-related death with varied prevalence worldwide.\textsuperscript{5} The estimated incidence of new HCC cases is 500 000-1 000 000 per year, with 600 000 annual deaths globally. Most cases of HCC occur in Asia, particularly in East Asia where several countries have a very high incidence of over 20 cases/100 000 populations. Its incidence is 99 per 100 000 persons in Mongolia, 49 per 100 000 in Korea, 29 per 100 000 in Japan, and 35 per 100 000 in China, while Hong Kong and Thailand also have similarly high rates. Sub-Saharan Africa is the next region with high HCC incidence, particularly the western region, including Gambia, Guinea, and Mali, and also the Republic of Mozambique in south-east. Countries with moderately high risk of 11 to 20 cases/100 000 include Italy, Spain and Latin American countries, while those with intermediate risk of 5 to 10 cases/100 000 include France, the United Kingdom, and Germany. Relatively low incidence of less than 5 cases/100 000 is recorded in the United States, Canada, and Scandinavia. However in many areas of the world the incidence is unknown.\textsuperscript{94}

In a ten year study of 22 450 Egyptian patients with CLD, 5.9% had HCC and unlike other African nations 72.3% of these were associated with HCV and only 20.4% were HBV
infection seropositive. This is not surprising, because Egypt has the highest HCV prevalence in
the world. In Nigeria, reports show variable geographic prevalence. In Jos it was the 5th
commonest cancer while Nwokediuko S et al reported that HCC constituted 9.7% of all
cancers diagnosed in Enugu during their study period. It accounted for 3.8% of the total
malignancies in a report from PortHarcourt of which 84.0% of their studied patients had
concomitant cirrhosis. Reports from Ilorin, Ibadan, Ife and Enugu revealed that HCC is the
commonest cause of liver disease, however in Maiduguri, Kano, Zaria and Jos it is second to
chronic hepatitis. Chronic infection with HBV, HCV or both is the most common cause globally. Among
Western populations; alcohol-induced liver injury is a leading cause of liver cirrhosis and
constitutes the most important HCC risk. In Southern China and sub-Saharan Africa, dietary
ingestion of high levels of aflatoxin may present a special environmental hazard, particularly
in individuals chronically infected with HBV. Other exogenous factors have also been
criminated, including iron overload, long-term use of oral contraceptives, and high-dose
anabolic steroids. The development of liver cirrhosis, particularly in association with
inherited genetic diseases such as alpha-1-antitrypsin deficiency or haemochromatosis places
the individual at a greater risk of HCC development. Risk is also increased if aetiological risk
factors exist in combination e.g., HCV infection and alcohol use or HBV infection and
exposure to aflatoxin. In Nigeria, the most important aetiologic risk factor is chronic
infection with HBV. This infection rate ranges from 49% (Gombe), 54.7% (Ekiti), 61% (Ife),
61.5% (Enugu), 67% (Maiduguri) to 86.5% (Kano). The laboratory findings are in part determined by the underlying liver disease and are non
specific. Elevations of various liver enzymes such as aspartate amino transferase (AST),
alanine aminotransferase (ALT), alkaline phosphatase (AP), gamma-glutamyl-transpeptidase
(GGT) and bilirubin are often recorded. A significantly raised level of alpha-fetoprotein
(AFP) of > 500 ng/ml or continuously rising values even if less than 100 ng/ml, strongly
suggests HCC. However, not all cases of HCC are associated with AFP elevation since raised
AFP may also be found in liver disease without HCC. Furthermore, in the early stages of
HCC development, AFP levels do not closely correlate with clinical HCC stage. AFP levels,
therefore, have to be interpreted individually in the context of other clinical symptoms and
signs as well as imaging studies. Another HCC-specific marker is des-gamma-
carboxyprothrombin (DCP) which is roughly equivalent to AFP. Occasionally, HCC patients
develop a paraneoplastic syndrome with erythrocytosis, hypoglycaemia or hypercalcaemia.
Imaging studies are important in patient management for the identification and localization of HCC. The standard imaging techniques are ultrasonography and computerised tomography (CT) and magnetic resonance imaging (MRI) for tumour detection and staging.

Morphologically, the tumour mass may be unifocal, multifocal or diffusely infiltrative, permeating widely and sometimes involving the entire liver. All three patterns may cause liver enlargement, particularly the large unifocal and multinodular patterns. The diffusely infiltrative tumour may blend imperceptibly into a cirrhotic liver background. Microscopically, the tumour varies from well-differentiated to highly anaplastic undifferentiated lesions. In well-differentiated and moderately differentiated tumours, 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, 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. Fibrolamellar carcinoma is a distinct variant of HCC that constitutes 5% of HCC cases and occurs in young adults aged 20 to 40 years with equal sex incidence. Usually there are no underlying chronic liver diseases, though the prognosis is better than the conventional HCC. Morphologically, it is often a single large, hard “scirrhous” tumor with fibrous bands coursing through it. Histologically it is composed of well-differentiated polygonal cells growing in nests or cords, separated by parallel lamellae of dense collagen bundles. 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.\textsuperscript{2, 67, and 103}

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, α1-anti-trypsin and Alfa-Fetoprotein. In cases of poorly differentiated tumours, such markers display insufficient performance and additional markers are useful. Among them, Glypican-3 (GPC-3), an oncofetal protein, seems to be the more efficient with more than 80 \% of HCC immunopositive. Interestingly, immunphenotypotyping, based on a panel of antibodies, has shown its performance in the differential diagnosis of early HCC and dysplastic nodules.\textsuperscript{104} Additionally; genomic studies provided molecular classifications of HCC based on gene expression. Such analysis allowed the identification of subgroups of patients according to aetiological factors, stage of the disease, recurrence and
survival. Major classes of tumours emerging from these comprehensive analyses are also related to important carcinogenesis pathways such as activation of β-catenin, AKT/mTOR, or inactivation of TP53 and RB1.67, 105-107

1. G1 tumours show low HBV copy number and overexpression of genes expressed in fetal liver and controlled by parental imprinting.
2. G2 tumours have high HBV copy number, and mutations of PIK3CA and TP53.
3. G3 tumours are TP53 mutated, lack HBV infection, and show frequent P16 methylation as well as overexpression of genes controlling the cell cycle.
4. G4 tumours are heterogeneous, including TCF1 mutated adenomas and carcinomas.
5. G5 tumours show CTNNB1 (β-catenin) mutations leading to Wnt pathway activation.
6. G6 tumours show CTNNB1 (β-catenin) mutations leading to Wnt pathway activation, as well as satellite nodules, higher activation of the Wnt pathway and E-cadherin underexpression.

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.

Edmondson and Steiner system, divided HCC into four grades from I to IV on the basis of histological differentiation.

- Grade I: is the well differentiated tumour consisting of small tumour cells arranged in thin trabeculae.
- Grade II: Cells are larger with abnormal nuclei and glandular structures may be present.
- Grade III: this has larger and more hyperchromatic nuclei and cytoplasm is granular and acidophilic, but less than grade II.
- Grade IV: tumour cells are much poorly differentiated with hyperchromatic nuclei and loss of trabecular pattern.

The important prognostic factors of HCC are related to
- tumour stage (number and size of nodules, presence of vascular invasion and extrahepatic spread), tumour size is a major prognostic factor, with a very good prognosis for small or minute carcinomas
- liver function (defined by Child–Pugh’s class, bilirubin, albumin, portal hypertension)
- General health status of the patient.
CHAPTER FOUR

MATERIALS AND METHOD

This was a ten year retrospective analysis of all the liver biopsies submitted to the Department of Pathology, Ahmadu Bello University Teaching Hospital (ABUTH) Shika-Zaria, from 1st January, 2004 to 31st December 2013. The hospital is a referral and tertiary center in Kaduna state, Northwestern region of the country and renders specialist medical services to the patients within the state and from neighbouring states of Sokoto, Zamfara, Kano, Jigawa, Bauchi, and Niger. In particular the hospital offers specialist care in the management of liver diseases under the expertise of trained Gastroenterologists.

All submitted liver biopsies were extracted from the surgical biopsy records of the department. Relevant histology stained slides were retrieved, viewed and reviewed with supervising consultants. Freshly stained slides were made from stored paraffin embedded tissue blocks in cases of missing slides.

Special stains such as Masson’s trichrome, Reticulin, Periodic acid-Schiff (PAS) with and without diastase digestion, Perls and Shikata orcein, were used. Reticulin stain was used for accurate assessment of structural changes because it demonstrates type III collagen and highlights hepatic plate architecture as well as thin layers of connective tissue and early cirrhosis. The stain is also highly sensitive in the detection of early fibrosis and thus was employed in the staging of chronic viral hepatitis cases. Masson trichrome stain demonstrates type I collagen, Mallory hyaline bodies and mega mitochondria in alcoholic liver disease. PAS was used to demonstrate the presence of mucin, extent of hepatocyte loss in the grading of necro-inflammatory activity (focal lytic necrosis) and to highlight presence of granuloma formation as well as to accentuate hypertrophied Kupffer cells filled with ceroid pigment in
cholestasis. Perls’ stain was used to demonstrate stainable iron while Orcein stain demonstrated hepatitis B surface material (HBsAg) within hepatocytes.

Patients’ bio-data including age and sex were extracted from the accompanying case cards. Other information on viral load and or positivity was also extracted from case cards. Aetiology/ aetiologic factors will be based on clinical history e.g. significant alcohol consumptions, serological test like HBsAg, HCVab and viral load as documented on the case cards and augmented with histologic features like HBV viral cytoplasmic particles using orcein histochemical stains.

All cases of viral hepatitis was graded using Ishak modified histological activity index (HAI) and the Liver Biopsy Report Pro-forma proposed by the Society for Gastroenterology and Hepatology in Nigeria (SOGHIN) 2012 Conference (Appendices II and III). 64, 67

Analysis of the collected data was carried out using Statistical Program for Social Sciences (SPSS) Version 16.0. Data was presented in frequency distribution tables and figures including photomicrographs with legends.

Ethical clearance for the study was obtained from the Ethics and Scientific Committee of the Ahmadu Bello University Teaching Hospital, Shika-Zaria.
INCLUSION CRITERIA

All diagnosed cases of liver disease from the liver biopsies submitted to the Department of Pathology within the study period were included.

EXCLUSION CRITERIA

- Cases with missing request cards, tissue blocks and slides were excluded from the study.
- All fine needle aspiration specimens were excluded.
- All ultrasound guided fine needle aspiration biopsies were excluded.
- All postmortem liver samples were excluded.
- All inadequate liver biopsies as defined by the set criteria were excluded.

LIMITATIONS OF THE STUDY

This study was hospital based and may not represent the actual distribution pattern and extent of liver disease in the general population.
CHAPTER FIVE

RESULTS

Three hundred and thirty four (334) liver biopsy specimens were received in the Department of Pathology, Ahmadu Bello University Teaching Hospital (ABUTH) Zaria, during the 10-year study period. Of these, three hundred and one (301) cases fulfilled the study criteria and constituted 1.2% of all the specimens received in the same period (fig. 1).

There were 197 males and 104 females with a male: female ratio of 1.9:1. Their ages ranged from 2 months to 80 years with a peak age incidence in the 3rd decade of life, while children aged 10 years and below constituted 5.0% of all the cases (Tables 1).

The liver diseases were categorized into congenital (2.3%), infectious conditions (2.9%), hepatitis (56.5%), cirrhosis (15.3%) and neoplastic diseases (18.9%). Others included alcoholic liver disease (0.3%) and cholestasis (0.3%). The congenital lesions recorded were biliary atresia with a predominant female distribution and an age range of 2 to 7 years and an inflamed solitary cyst in a 47-year-old female. Of the infection category, there were 4 cases each of tuberculosis and schistosomiasis (Table: 1), microscopically, schistosoma ova were seen within granuloma surrounded by hepatocyte plates.

The hepatitis group was the commonest and consisted of chronic viral hepatitis (55.2%) neonatal hepatitis (1.0%) and a solitary case of acute suppurative hepatitis in a 1-year-old male child. There were one hundred and sixty six cases of chronic viral hepatitis with a male to female distribution of 119 to 47 (M: F; 2.5:1). Of these, 137 (82.5%) cases occurred in ages 21 years to 50 years and peaked in the third decade of life (Table 2). These cases of chronic viral hepatitis were reviewed microscopically and graded using the modified Ishaq histologic activity index criteria and of the 166, forty seven (28.3%) cases were graded minimal disease, 70 (42.2%) cases were mild grade disease while 45 (27.1%) and 4 (2.4%) cases had moderate and severe grade disease respectively (Tables 3, fig 2). The stages of disease progression is
represented in Table 4 which showed that a bulk of 70.5% cases were between stages 0-2 and 25.9% of cases were stage 3-4 while only 6% were in stage 5.

Neoplastic lesions constituted 18.9% of all cases and include a case of liver cell adenoma in a 20 years old female, forty-one (41) cases of hepatocellular carcinoma (HCC), 4 cases of hepatoblastoma and 11 cases of metastatic tumours with primary in the gastrointestinal tract (6), ovary (2), breast (2) and an unknown site from a 45 year old man. HCC showed a male preponderance with a male to female ratio of 1.3:1 and peak age distribution in the 4th decade of life. The youngest patient with HCC was a 15 years old male. Nineteen (46.3%) of the HCC patients also had associated cirrhosis. All the four cases of hepatoblastoma were seen in children; a 19 month old female and three males aged 2, 12 and 12 years old respectively (Table 2).

Liver cirrhosis was the second most common disease and accounted for 15.3% of all the cases with a male to female ratio of 1.7:1 and peak age in the fifth decade of life (Tables 1 and 2). Hepatotropic viruses, as indicated by the serological tests, accounted for the bulk of aetiological factors with HBV infection seen in 19 (41.3%) of the cases, HCV in 4 (8.7%) and HBV/HCV co-infection in 2 (4.4%) cases. Biliary type cirrhosis secondary to biliary atresia accounted for 3 (6.5%) of cases and this was seen in children aged 3 to 7 months with a female preponderance. The cryptogenic cirrhosis cases (32.6%) had no identifiable aetiologic agent clinico-pathologically. Only 3 cirrhotic cases (6.5%) were associated with history of significant alcohol consumption (Table 5).

Other liver pathologies included Steatosis and steatohepatitis, alcoholic liver disease and cholestasis (Table 2).
Figure 1: Line Graph showing Annual Distribution of Livers Biopsies from 2004 to 2013
### Table 1: Distribution of all Liver Diseases by Gender

<table>
<thead>
<tr>
<th>Liver Disease</th>
<th>Sex Distribution</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td><strong>Congenital</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biliary atresia</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Inflammatory cyst</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Specific Infectious conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Schistosomiasis</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td><strong>Hepatitis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic viral hepatitis</td>
<td>119</td>
<td>47</td>
</tr>
<tr>
<td>Neonatal hepatitis</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Acute suppurative hepatitis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Alcoholic liver disease</strong></td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Steatosis/steatohepatitis</strong></td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td><strong>Cholestasis</strong></td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Cirrhosis</strong></td>
<td>29</td>
<td>17</td>
</tr>
<tr>
<td><strong>Neoplastic diseases</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Benign</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver cell adenoma</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Malignant</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>23</td>
<td>18</td>
</tr>
<tr>
<td>Hepatoblastoma</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Metastatic tumours</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td><strong>Total (%)</strong></td>
<td><strong>197 (65.5)</strong></td>
<td><strong>104 (34.5)</strong></td>
</tr>
</tbody>
</table>
### Table 2: Age Distribution of all Liver Diseases

<table>
<thead>
<tr>
<th>Liver diseases</th>
<th>Age in years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-10</td>
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<tr>
<td><strong>Congenital</strong></td>
<td></td>
</tr>
<tr>
<td>Biliary atresia</td>
<td>7</td>
</tr>
<tr>
<td>Inflammatory cyst</td>
<td>0</td>
</tr>
<tr>
<td><strong>Hepatitis</strong></td>
<td></td>
</tr>
<tr>
<td>Chronic viral hepatitis</td>
<td>1</td>
</tr>
<tr>
<td>Neonatal hepatitis</td>
<td>3</td>
</tr>
<tr>
<td>Acute suppurative hepatitis</td>
<td>1</td>
</tr>
<tr>
<td><strong>Infectious conditions</strong></td>
<td></td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>0</td>
</tr>
<tr>
<td>Schistosomiasis</td>
<td>0</td>
</tr>
<tr>
<td><strong>Cirrhosis</strong></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td><strong>Alcoholic liver disease</strong></td>
<td>0</td>
</tr>
<tr>
<td><strong>Steatosis/steatohepatitis</strong></td>
<td>1</td>
</tr>
<tr>
<td><strong>Cholestasis</strong></td>
<td>0</td>
</tr>
<tr>
<td><strong>Neoplastic diseases</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Benign</strong></td>
<td></td>
</tr>
<tr>
<td>Liver cell adenoma</td>
<td>0</td>
</tr>
<tr>
<td><strong>Malignant</strong></td>
<td></td>
</tr>
<tr>
<td>Hepatocellular</td>
<td>0</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>0</td>
</tr>
<tr>
<td>Hepatoblastoma</td>
<td>2</td>
</tr>
<tr>
<td>Secondary tumours</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>18</strong></td>
</tr>
</tbody>
</table>
**Table 3:** Chronic Viral Hepatitis Review Using the Ishaq Modified HAI*

<table>
<thead>
<tr>
<th>Previous Diagnosis</th>
<th>Frequency</th>
<th>Minimal</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Persistent Hepatitis</td>
<td>52</td>
<td>35</td>
<td>16</td>
<td>1</td>
<td>0</td>
<td>52</td>
</tr>
<tr>
<td>Chronic Persistent Hepatitis with Fatty Change/portal triaditis</td>
<td>11</td>
<td>5</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Chronic Active Hepatitis</td>
<td>21</td>
<td>0</td>
<td>5</td>
<td>14</td>
<td>2</td>
<td>21</td>
</tr>
<tr>
<td>Chronic Lobular Hepatitis</td>
<td>12</td>
<td>2</td>
<td>6</td>
<td>4</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>Chronic Lobular Hepatitis with Fatty change/Steatosis</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Chronic Viral Hepatitis</td>
<td>28</td>
<td>0</td>
<td>16</td>
<td>11</td>
<td>1</td>
<td>28</td>
</tr>
<tr>
<td>Chronic Viral Hepatitis with Portal Inflammation</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
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<tr>
<td>Chronic Hepatitis With Activity/Fatty Change</td>
<td>4</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Chronic Hepatitis B Viral Hepatitis</td>
<td>14</td>
<td>2</td>
<td>8</td>
<td>3</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>Chronic Hepatitis B Viral Hepatitis with Activity/Fibrosis</td>
<td>8</td>
<td>1</td>
<td>6</td>
<td>1</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Hepatitis C Viral Infection</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Portal / Periportal Triaditis</td>
<td>5</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>With Fibrosis/Steatosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 0/ Stage 1 Hepatitis</td>
<td>6</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>166</strong></td>
<td><strong>47</strong></td>
<td><strong>70</strong></td>
<td><strong>45</strong></td>
<td><strong>4</strong></td>
<td><strong>166</strong></td>
</tr>
</tbody>
</table>

* HAI= histologic activity index
Figure 2: Histogram showing Grading of Chronic Viral Hepatitis Using Ishaq’s Modified HAI
**Table 4:** Staging of Chronic Viral Hepatitis by Sex using Ishaq Modified HAI*

<table>
<thead>
<tr>
<th>Grade</th>
<th>STAGE</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>F</td>
</tr>
<tr>
<td>Minimal</td>
<td>18</td>
<td>14</td>
</tr>
<tr>
<td>Mild</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Moderate</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Severe</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>28</td>
<td>17</td>
</tr>
<tr>
<td>Grand total</td>
<td>45</td>
<td>37</td>
</tr>
<tr>
<td>(%)</td>
<td>(27.1)</td>
<td>(22.3)</td>
</tr>
</tbody>
</table>

*HAI= Histologic activity index
Figure 3: Pie Chart showing Aetiological Factors associated with Cirrhosis from Serological Tests and Clinical History
Figure 4: Mild portal and periportal/ periseptal interface inflammation. (PAS X 400)
Figure 5: Modified Ishaq Stage 1; Fibrous expansion of portal tract (Masson Trichrome X 400)
**Figure 6:** Moderate lobular inflammation (lytic necrosis) in a moderate grade disease (H & E X 100)
**Figure 7:** A Modified Ishaq Stage 4 showing Fibrous expansion of portal areas with marked portal-to-portal as well as portal-to-central bridging (Reticulin stain X 400)
Figure 8: Liver cirrhosis showing round nodules (Reticulin stain X100)
Figure 9: A & B Secondary biliary cirrhosis showing irregular nodules (M T; A X100, B X 400)
Figure 10: Well differentiated Hepatocellular carcinoma (H & E X100)
Figure 11: Hepatoblastoma, showing polygonal epithelial cells forming acini. (H &E X 100)
Figure 12: A and B. Metastatic Adenocarcinoma (H & E A x 100, B x 400)
CHAPTER SIX

DISCUSSION

The predominant liver disease seen in this study was chronic viral hepatitis (CHV) similar to other reports in parts of northern Nigeria.\textsuperscript{14-17,92} Hepatocellular carcinoma which was the second most common in this study, is the predominant liver disease in Ilorin (north central), Ibadan, Ile-Ife and Lagos, all in southwest Nigeria.\textsuperscript{18, 88-91} David et al, in their study of the safety of liver biopsy in the same center as the index study also reported chronic viral hepatitis as the predominant liver pathology.\textsuperscript{15}

Chronic viral hepatitis accounted for 55.2\% of all the liver diseases recorded in this study. This is slightly higher though comparable to the frequency distribution of 40.5\% and 45.7\% respectively from Kano (North West) and Maiduguri (North East).\textsuperscript{14,16} The lowest frequency rate of 31.7\% was reported from Jos, North Central while the highest rate of 62.5\% was reported by Ugiagbe et al in Benin, South-South Nigeria.\textsuperscript{17} This higher figure was according to the authors attributable to lack of HBV vaccinations. Other factors that may explain these different frequency rates are the regional differences in the incidence of HBV and HCV infections.

Over 80\% of the CVH cases affected young to middle aged individuals, the life force of any economically vibrant population. Our peak age frequency was in the 3\textsuperscript{rd} decade with 44.6\% cases and this is a decade earlier than that reported from Lagos, South West by Abdulkareem et al.\textsuperscript{18}

The CVH cases were reviewed based on Ishaq modified HAI, a comprehensive quantitative numerical assessment. One hundred and seventeen cases (70.5\%) had minimal and mild grade diseases with scores of 1-3 and 4-8 respectively according to Desmet et al.\textsuperscript{108} also 70.5\% of the cases had fibrosis score of 0-2, a non-progressive disease with only 3.6\% having a score of 5 which is an advanced stage that may progress to cirrhosis. However, adequate
treatment at this stage can still reverse the process with promising results. Our finding is comparable to the report by Okafor and Olusegun in Ile-Ife who used similar grading and staging criteria in their study of 50 cases and documented 23 minimal and 19 mild grade diseases with respective scores of 1-3 and 4-8 while 35 cases had fibrosis score of 0 with only 1 case of stage 5 disease. Ananya et al in their study of chronic HCV hepatitis also reported that 60.5% of their cases had Ishaq HAI score of less than 8, a minimal to mild grade disease, 33.3% had fibrosis stage 0 to 2 disease which required no antiviral or interferon treatment and 66.7% had fibrosis stage 3. Similarly, a prospective study of three hundred and forty four (344) cases of chronic HCV patients in Pakistan by Anwar et al, reported 54.9% patients with minimal to mild disease activity. In the later study, they also reported that 69.0% of their cases had stage 0-2 disease, a finding which is similar to 70.5% recorded in this study for stage. with stage 0-2 in this study. Only 8.7% of their patients were stage 4 disease which is definite cirrhosis. The finding of 70.5% for minimal to mild grade in this study also concur with reports from Brazil and Dhaka, Bangladesh by Atique et al where they recorded 63% for stages 0-2 though with wide disparity in the disease grades. The low rate of progression of disease in this study may be due to low HCV genotype in the study population. According to the World Health Organization reports, 75% of adult infected with HCV progress to chronic disease while only 5.5% to 10% with chronic HBV hepatitis progress. The fibrosis stage of CVH determined progression to cirrhosis and possible transformation to HCC, in our series 10.8% of cases had modified Ishaq HAI stages 4-5 and these are likely to progress to cirrhosis with significant percentages transforming to HCC.

Liver cirrhosis was the second most common liver disease recorded in this study. It represented 15.3% of the cases seen and had a male preponderance with a peak age distribution in the 5th decade of life. This is similar to the reports from Kano, Jos, Ibadan,
Lagos and Enugu though a decade earlier to report by Adeniji et al from Ilorin. The regional variations of liver cirrhosis in Nigeria may be attributed to religious and cultural reasons of alcohol consumption as well as degree of exposure to the other associated risk factors. The predominant clinicopathologically determined aetiological factors associated with cirrhosis in this study were HBV infection (41.3%), HCV infection (8.7%) and alcohol (6.5%). Thirty two point six percent (32.6%; 15 cases) were cryptogenic and had no identifiable risk factor. In a study of 47 liver cirrhosis cases by Lawan and Ogunbiyi in Ibadan, 7 and 2 cases had morphological evidence of HBV and HCV infections respectively. In United Kingdom, a study reported 38.7% of 3360 cases were due to chronic alcoholism with only 5.4% due to viral hepatitis and 7.1% due to autoimmune hepatitis which is rare in our setting.

Granulomatous hepatitis secondary to tuberculosis and schistosomiasis accounted for 1.3% respectively in our study. In Ibadan, specific granulomatous inflammation of the liver constituted 6.2% of the 632 liver biopsies studied, while, in Lagos only 0.6% of their 345 cases of liver biopsy studied form specific granulomatous inflammation. In another study of paediatric liver biopsies in Jos, 37.5% of the 48 cases of liver dysfunctions were due to hepatic schistosomal fibrosis.

HCC was the most common neoplastic liver disease accounting for 73.2% of the liver neoplasm and constituted 13.6% of all liver pathologies in this study. This is comparable to a study in which 12.5% was reported from Benin, South South Nigeria. It is however lower than other reports with increasing rates ranging between 15.5% - 45.5% from Zaria, Kano, Ile-Ife, Jos, Lagos, Ilorin, Enugu and Ibadan respectively. Our finding of 73.3% for HCC of all liver tumours concurs with reports from Lagos South West, Nigeria by
Abdulkareem F B et al who in their comprehensive review of hepatic neoplastic diseases recorded that 80% of the 118 cases were HCC.\textsuperscript{115}

The male to female ratio in our study showed a male preponderance similar to reports from Bangladesh, Egypt and Benin and Port Harcourt from Nigeria.\textsuperscript{17, 84, 92, 96} However, a peak age in the 4\textsuperscript{th} decade of life in this study is a decade earlier than most reports from within and outside Nigeria.\textsuperscript{18, 86, 95, 98}

Only nineteen (46.3\%) of these HCC cases were post-cirrhotic. Post cirrhotic HCC were reported in 30\% of cases from Lagos, 78\% cases from Ile-Ife and 66.2\% cases from Tanzania by Hyasinta J et al.\textsuperscript{18, 89, 90} There is a strong evidence for the pathogenetic role of hepatotropic viruses in the development of HCC through the cirrhotic liver. This is the case for both HBV and HCV, and for both adult and pediatric patients.\textsuperscript{2, 67} Hepatotropic viral hepatitis is the leading cause of liver cirrhosis associated hepatocellular carcinoma. In one series from Japan, the development rate of hepatocellular carcinomas after a 15-year observation period was 27\% in hepatitis B and 75\% in hepatitis C.\textsuperscript{67} The incidence of hepatitis B and/or hepatitis C surface antigenemia in patients with HCC is over 90\%, both in the United States and overseas with significant percentage associated with cirrhosis.\textsuperscript{67, 94}

Associated risk factors identified in this study were serological evidence of HBV infection in 16 cases (39.0\%), HCV infection in 8 cases (19.5\%) and HBV/HCV co-infections in 4 male patients. The sero-prevalence of HBsAg in Nigeria ranges from 10\% to 40\% and that of HCV from 4.5\% to 5\%.\textsuperscript{114}

In developed nation’s obesity, ALD, HCV and NAFLD are the leading aetiologic factors in the causation of HCC.\textsuperscript{94} Obesity is a global public health problem particularly in developed countries and it is also an important risk factor for NAFLD. Non-alcoholic steatohepatitis (NASH) is a well-recognized clinico-pathologic syndrome that occurs primarily in obese women with diabetes mellitus and it has histological similarities to alcoholic liver disease in
the absence of significant alcohol consumption. It is known to progress to cirrhosis and HCC, though the exact mechanism remains obscured. Hyper-insulinaemia with insulin resistance and its antecedent molecular consequences were the culprit in the pathogenesis of HCC in NASH. Increasing westernization and adoption of indolent lifestyle may thus pose another danger of increase incidence of HCC in our environment. There was no known aetiological cause in 31.7% of cases which is in conformity with the available literature that one quarter of HCC cases have no known aetiologic risk factor.

Metastatic tumours to the liver constituted 3.7% of this study. Similar frequency rates of metastatic diseases were documented in Jos (4.4%), Benin (7.5%) and Lagos (9.5%). These tumours had primary in the gastrointestinal tract, ovary and breast. These are known to metastasize to the liver. Only one case had no known primary site. Identification of primary site of a malignant tumoural mass in the liver poses challenge, however clinicopathologically this can be ratified. Morphologically well differentiated HCC may be differentiate from tumour of other sites, however poorly differentiated tumours will always pose a challenge, but with good H and E and panel of immunohistochemical antibody makers most of this tumour can be identified.

One of such marker is Hep Par 1, however this marker can not differentiate benign from malignant lesions of the liver but can differentiate primary from metastatic lesions. The sensitivity of Hep Par1 in establishing the diagnosis of HCC can be increased by using it in combination with a panel of other markers such as polyclonal CEA, AFP, and cytokeratins (CK). HCC stain with CK 8 and 18 (CAM5.6) though is positive in most epithelial tumours, but HCC is negative for CK 7 except fibrolamellar type which shows positivity. CK 8 is positive in all the carcinoma of simple epithelia and malignant melanoma stains both CK 8 and 18. Ovarian epithelial cancer show positivity for CK 7, GIT cancer react to CK 20 while
breast cancers will show ER, PR and Her 2 positivity depending on the molecular class of the tumour, the basal like type react with CK 7.67, 105-107

Children less than 10 years of age accounted for 6.0% of this study population. They had biliary atresia (7 cases; 38.9%), neonatal hepatitis (3 cases; 16.7%), cryptogenic cirrhosis (3 cases; 16.7%) and hepatoblastoma (2 cases; 11.1%). We recorded no hepatic infection in this age group in sharp contrast with report from Jos by Obafunwa et al where hepatic schistosomal fibrosis predominated.11 Our report is however in conformity with the report from Ga-Rankuwa, South Africa by M. N. Muthuphe10 in their study of childhood liver diseases that documented biliary atresia in 20.8%, neonatal hepatitis in 19.4% and cirrhosis in 16.6% cirrhosis. Metabolic liver disorder was not seen in our study, in contrast to Seyed M D et al study in Iran, who reported chronic hepatitis (23.1%), metabolic disorders (including hereditary tyrosinemia type 1, glycogen and lipid storage diseases) (12.1%), cirrhosis (8.8%) and neonatal hepatitis (7.1%) as the commonest liver diseases with biliary atresia accounting for only 4.5% of their study.40 Another report by Akinbami in Muscat, Oman on 67 paediatric liver biopsies recorded neonatal hepatitis (28.9%), biliary atresia (11.8%) and cirrhosis (9.2%) as the predominant liver pathology, thus confirming biliary atresia, neonatal hepatitis and cirrhosis as the commonest paediatric liver diseases.43

Hepatoblastoma, a primary malignant neoplastic liver disease in children with dismal prognosis accounted for all the neoplastic lesions in this age group similar to other reports.9-11, 40-43, 45

Hepatoblastoma is the most common primary liver cancer in children and usually occur at a very young age of three and below, and are of embryonal or congenital origin.2, 116 It has been associated with some congenital abnormalities such as hemihypertrophy, nephroblastoma, glycogen storage disease, and familial colonic polyposis.67 In our study, we recorded 2 cases
below 2 years and the other two cases were 12years each. This finding is comparable to reports of three cases aged 2months, 14months and 10year old by Sinniah et al from Malasia.\textsuperscript{117} Atimati et al also reported a 16 0ld girl with hepatoblastoma from Benin city, Nigeria.\textsuperscript{118}

The diagnosis of hepatoblastoma is usually made by histology of liver biopsy and supportive investigations include assay for \( \alpha \)-fetoprotein, abdominal ultrasonography, computerized tomography and magnetic resonance imaging. The tumour is mainly unifocal, well circumscribed affecting the right lobe more commonly than the left, but occasionally affects both lobes and can be multifocal.

There are two primary histologic variants of hepatoblastoma: The epithelial type composed of either small polygonal foetal cells or smaller embryonal cells forming acini, tubules and papillary structures simulating liver development and; the mixed type which is composed of epithelial and mesenchymal, structures such as primitive mesenchyme, osteoid, chondroid and striated muscle fibres. All our cases were of the epithelial type.

The treatment of hepatoblastoma is surgical resection with adjuvant chemotheraphy. The prognosis depends on the tumour localisations and premorbid condition of the patient but better in younger than the older and adolescent childrens.\textsuperscript{2, 67, 118}

**CONCLUSIONS**

The most common liver diseases in Zaria are hepatitis, cirrhosis and hepatocellular carcinoma. All showed a slight male preponderance with peak age of affectionation in the third decade of life. Hepatotropic viruses, hepatitis B virus (HBV) and hepatitis C virus (HCV) were the main implicated aetiologic factors in majority of our cases while mild grade disease of chronic viral hepatitis accounted for bulk of the cases reviewed
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APPENDIX I

CLASSIFICATION OF LIVER DISEASES

The World Health Organization (WHO), International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) Version for 2010 will be used.\textsuperscript{105}

A. Alcoholic Liver Disease
   1. Alcoholic fatty liver
   2. Alcoholic hepatitis
   3. Alcoholic fibrosis and sclerosis of liver
   4. Alcoholic cirrhosis of liver
      Including: Alcoholic cirrhosis not otherwise specified (NOS)
   5. Alcoholic hepatic failure
      Including:
      \begin{itemize}
      \item Alcoholic hepatic failure:
      \item Alcoholic hepatic failure NOS
      \item Acute Alcoholic hepatic failure
      \item Chronic Alcoholic hepatic failure
      \item Subacute Alcoholic hepatic failure, with or without hepatic coma
      \end{itemize}
   6. Alcoholic liver disease, unspecified

B. Toxic Liver Disease:

Including:
   \begin{itemize}
   \item Drug-induced: idiosyncratic (unpredictable) liver disease and
   \item Toxic (predictable) liver disease
   \end{itemize}

Excluding:
   \begin{itemize}
   \item Alcoholic liver disease and
   \item Budd-Chiari syndrome
   \item Toxic liver disease with cholestasis; Including: Cholestasis with hepatocyte injury and "Pure" cholestasis
   \item Toxic liver disease with hepatic necrosis; Including: Hepatic failure (acute or chronic) due to drugs
   \item Toxic liver disease with acute hepatitis
   \item Toxic liver disease with chronic persistent hepatitis
   \item Toxic liver disease with chronic lobular hepatitis
   \item Toxic liver disease with chronic active hepatitis; Including: Toxic liver disease with lupoid hepatitis
   \item Toxic liver disease with hepatitis, not elsewhere classified
   \item Toxic liver disease with fibrosis and cirrhosis of liver
   \item Toxic liver disease with other disorders of liver; Including: Toxic liver disease with:
• focal nodular hyperplasia
• hepatic granulomas
• peliosis hepatis
• veno-occlusive disease of liver
10. Toxic liver disease, unspecified

C. Hepatic Failure Not Elsewhere Classified
   Including

• Hepatic, coma NOS and encephalopathy NOS hepatitis:
  i. acute (not elsewhere classified) with hepatic failure
  ii. fulminant (not elsewhere classified) with hepatic failure
  iii. malignant (not elsewhere classified) with hepatic failure
• liver (cell) necrosis with hepatic failure
• yellow liver atrophy or dystrophy

Excluding:
  ➢ alcoholic hepatic failure
  ➢ hepatic failure complicating:
    abortion or ectopic or molar pregnancy
    pregnancy, childbirth and the puerperium
  ➢ icterus of fetus and newborn
  ➢ viral hepatitis
  ➢ with toxic liver disease
1. Acute and subacute hepatic failure
2. Chronic hepatic failure
3. Hepatic failure, unspecified

D. Chronic Hepatitis Not Elsewhere Classified

Excluding:
  hepatitis (chronic):

• alcoholic
• drug-induced
• granulomatous
• reactive, nonspecific
• viral
1. Chronic persistent hepatitis, not elsewhere classified
2. Chronic lobular hepatitis, not elsewhere classified
3. Chronic active hepatitis, not elsewhere classified
   Including: Lupoid hepatitis not elsewhere classified
4. Other chronic hepatitis, not elsewhere classified
5. Chronic hepatitis, unspecified

E. Fibrosis and Cirrhosis of Liver
Excluding:
  i. alcoholic fibrosis of liver
  ii. cardiac sclerosis of liver
  iii. cirrhosis (of liver):
      • alcoholic
      • congenital
      i. with toxic liver disease
      1. Hepatic fibrosis
      2. Hepatic sclerosis
      3. Hepatic fibrosis with hepatic sclerosis
      4. Primary biliary cirrhosis; Including: Chronic nonsuppurative destructive cholangitis
      5. Secondary biliary cirrhosis
      6. Biliary cirrhosis, unspecified
      7. Other and unspecified cirrhosis of liver
         Including: Cirrhosis (of liver):
      • NOS
      • cryptogenic
      • macronodular
      • micronodular
      • mixed type
      • portal
      • postnecrotic

F. Other Inflammatory Liver Diseases

Excluding:
  i. chronic hepatitis not elsewhere classified (NEC)
  ii. hepatitis:
      • acute or subacute
      • viral
      • toxic liver disease

1. Abscess of liver
   Including:
      a. Hepatic abscess:
         i. NOS
         ii. cholangitic
         iii. haematogenic
         iv. lymphogenic

      b. pylephlebitic

Excluding:
i. amoebic liver abscess
ii. cholangitis without liver abscess
iii. pylephlebitis without liver abscess

c. Phlebitis of portal vein
Including:
   • Pylephlebitis
Excluding:
   • pylephlebitic liver abscesses

2. Nonspecific reactive hepatitis
3. Granulomatous hepatitis, not elsewhere classified
4. Autoimmune hepatitis
5. Other specified inflammatory liver diseases
Including:
   • Nonalcoholic steatohepatitis (NASH)
6. Inflammatory liver disease, unspecified
Including:
   • Hepatitis NOS

G. Other Diseases Of Liver
Excluding:
   i. alcoholic liver disease
   ii. amyloid degeneration of liver
   iii. cystic disease of liver (congenital)
   iv. hepatic vein thrombosis
   v. hepatomegaly NOS
   vi. portal vein thrombosis
   vii. toxic liver disease

1. Fatty (change of) liver, not elsewhere classified
Including:
   • Nonalcoholic fatty liver disease (NAFLD)
Excluding:
   • Nonalcoholic steatohepatitis

2. Chronic passive congestion of liver
Including:
   i. Cardiac (so called) cirrhosis of liver
   ii. Cardiac sclerosis of liver

3. Central haemorrhagic necrosis of liver
Excluding:
   • liver necrosis with hepatic failure

4. Infarction of liver

5. Peliosis hepatis
Including:
   • Hepatic angiomatosis

6. Hepatic veno-occlusive disease
Excluding:
  - Budd-Chiari syndrome
7. Portal hypertension
8. Hepatorenal syndrome
   Excluding:
     - following labour and delivery
9. Other specified diseases of liver
   Including:
     i. Simple cyst of liver
     ii. Focal nodular hyperplasia of liver
     iii. Hepatoptosis
10. Liver disease, unspecified

H. Liver Disorders In Diseases Classified Elsewhere
1. Liver disorders in infectious and parasitic diseases classified elsewhere
   Including:
     i. Hepatitis:
        - cytomegaloviral
        - herpesviral [herpes simplex]
        - toxoplasma
     ii. Hepatosplenic schistosomiasis
     iii. Portal hypertension in schistosomiasis
     iv. Syphilitic liver disease
2. Liver disorders in other diseases classified elsewhere
   Including:
     Hepatic granulomas in:
     - berylliosis
     - sarcoidosis

NEOPLASTIC DISEASES
Epithelial tumours
Benign
  - Hepatocellular adenoma (liver cell adenoma)
  - Focal nodular hyperplasia
  - Intrahepatic bile duct adenoma
  - Intrahepatic bile duct cystadenoma
  - Biliary papillomatosis

Malignant
  - Hepatocellular carcinoma (liver cell carcinoma)
  - Intrahepatic cholangiocarcinoma (peripheral bile duct carcinoma)
  - Bile duct cystadenocarcinoma
- Combined hepatocellular and cholangiocarcinoma
- Hepatoblastoma
- Undifferentiated carcinoma

Non-epithelial tumours

Benign
- Angiomyolipoma
- Lymphangioma and lymphangiomatosis
- Haemangiomata
- Infantile haemangioendothelioma

Malignant
- Epithelioid haemangioendothelioma
- Angiosarcoma
- Embryonal sarcoma (undifferentiated sarcoma)
- Rhabdomyosarcoma
- Others

Miscellaneous Tumours includes;
- Solitary fibrous tumour
- Teratoma
- Yolk sac tumour (endodermal sinus tumour)
- Carcinosarcoma
- Kaposi sarcoma
- Rhabdoid tumour

Others are;

Haemopoietic and lymphoid tumours

Secondary tumours

Epithelial abnormalities; includes,
- Liver cell dysplasia (liver cell change)
- Large cell type (large cell change)
- Small cell type (small cell change)
- Dysplastic nodules (adenomatous hyperplasia)
- Low-grade
- High-grade (atypical adenomatous hyperplasia)
- Bile duct abnormalities
- Hyperplasia (bile duct epithelium and peribiliary glands)
- Dysplasia (bile duct epithelium and peribiliary glands)
- Intraepithelial carcinoma (carcinoma in situ)
Miscellaneous lesions

- Mesenchymal hamartoma
- Nodular transformation (nodular regenerative hyperplasia)
- Inflammatory pseudotumour
# APPENDIX II

**KNODELL Histological Activity Index**

<table>
<thead>
<tr>
<th>I. Periportal ± bridging necrosis</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>Mild piecemeal necrosis</td>
<td>1</td>
</tr>
<tr>
<td>Moderate piecemeal necrosis (involves less than 50 percent of the circumference of most portal tracts)</td>
<td>3</td>
</tr>
<tr>
<td>Marked piecemeal necrosis (involves more than 50 of most portal tracts)</td>
<td>4</td>
</tr>
<tr>
<td>Moderate piecemeal necrosis plus bridging necrosis</td>
<td>5</td>
</tr>
<tr>
<td>Marked piecemeal necrosis plus bridging necrosis</td>
<td>6</td>
</tr>
<tr>
<td>Multilobular necrosis</td>
<td>10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>II. Intralobular degeneration and focal necrosis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>Mild (acidophilic bodies, ballooning degeneration and/or scattered foci of hepatocellular necrosis in &lt; 1/3 of lobules or nodules)</td>
<td>1</td>
</tr>
<tr>
<td>Moderate (involvement of 1/3 to 2/3 of lobules or nodules)</td>
<td>3</td>
</tr>
<tr>
<td>Marked (involvement of &gt;2/3 of lobules or nodules)</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>III. Portal inflammation</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No portal inflammation</td>
<td>0</td>
</tr>
<tr>
<td>Mild (sprinkling of inflammatory cells in &lt;1/3 of portal tracts)</td>
<td>1</td>
</tr>
<tr>
<td>Moderate (increased inflammatory cells in 1/3 to 2/3 of portal tracts)</td>
<td>3</td>
</tr>
<tr>
<td>Marked (dense packing of inflammatory cells in &gt;2/3 of portal tracts)</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IV. Fibrosis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No fibrosis</td>
<td>0</td>
</tr>
<tr>
<td>Fibrous portal expansion</td>
<td>1</td>
</tr>
<tr>
<td>Bridging fibrosis (portal-portal or portal-central linkage)</td>
<td>3</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>4</td>
</tr>
</tbody>
</table>
APPENDIX III

A: Ishak Modified Histological Activity Index – grading: necroinflammatory scores

<table>
<thead>
<tr>
<th></th>
<th>SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Periportal or periseptal interface hepatitis (piecemeal necrosis)</strong></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td>Mild (focal, few portal areas)</td>
<td>1</td>
</tr>
<tr>
<td>Mild/moderate (focal, most portal areas)</td>
<td>2</td>
</tr>
<tr>
<td>Moderate (continuous around &lt;50% of tracts or septa)</td>
<td>3</td>
</tr>
<tr>
<td>Severe (continuous around &gt;50% of tracts or septa)</td>
<td>4</td>
</tr>
<tr>
<td><strong>B. Confluent necrosis</strong></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td>Focal confluent necrosis</td>
<td>1</td>
</tr>
<tr>
<td>Centrolobular necrosis in some areas</td>
<td>2</td>
</tr>
<tr>
<td>Centrolobular necrosis in most areas</td>
<td>3</td>
</tr>
<tr>
<td>Centrolobular necrosis + occasional portal–central (P-C) bridging</td>
<td>4</td>
</tr>
<tr>
<td>Centrolobular necrosis + multiple P-C bridging</td>
<td>5</td>
</tr>
<tr>
<td>Panlobular or multilobular necrosis</td>
<td>6</td>
</tr>
<tr>
<td><strong>C. Focal (spotty) lytic necrosis, apoptosis, and focal inflammation</strong></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td>One focus or less per 10× objective</td>
<td>1</td>
</tr>
<tr>
<td>One to four foci per 10× objective</td>
<td>2</td>
</tr>
<tr>
<td>Five to 10 foci per 10× objective</td>
<td>3</td>
</tr>
<tr>
<td>More than 10 foci per 10× objective</td>
<td>4</td>
</tr>
<tr>
<td><strong>D. Portal inflammation</strong></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>Mild, some or all portal areas</td>
<td>1</td>
</tr>
<tr>
<td>Moderate, some or all portal areas</td>
<td>2</td>
</tr>
<tr>
<td>Moderate/marked, all portal areas</td>
<td>3</td>
</tr>
<tr>
<td>Marked, all portal areas</td>
<td>4</td>
</tr>
<tr>
<td><strong>Maximum possible score for grading</strong></td>
<td><strong>18</strong></td>
</tr>
</tbody>
</table>
B: Ishak Modified Histological Activity Index – Staging: fibrosis scores

<table>
<thead>
<tr>
<th>Fibrosis</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>No fibrosis</td>
<td>0</td>
</tr>
<tr>
<td>Fibrous expansion of some portal areas, with or without short fibrous septa</td>
<td>1</td>
</tr>
<tr>
<td>Fibrous expansion of most portal areas, with or without short fibrous septa</td>
<td>2</td>
</tr>
<tr>
<td>Fibrous expansion of most portal areas with occasional portal-to-portal (P-P) bridging</td>
<td>3</td>
</tr>
<tr>
<td>Fibrous expansion of portal areas with marked portal-to-portal (P-P) as well as portal-to-central (P-C) bridging</td>
<td>4</td>
</tr>
<tr>
<td>Marked bridging (P-P and/or P-C) with occasional nodules (incomplete cirrhosis)</td>
<td>5</td>
</tr>
<tr>
<td>Cirrhosis, probable or definite</td>
<td>6</td>
</tr>
</tbody>
</table>
APPENDIX IV

Scheuer classification for grading and staging of chronic hepatitis

<table>
<thead>
<tr>
<th>Grade</th>
<th>Portal/periportal activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>1</td>
<td>Portal inflammation</td>
</tr>
<tr>
<td>2</td>
<td>Mild piecemeal</td>
</tr>
<tr>
<td>3</td>
<td>Moderate piecemeal</td>
</tr>
<tr>
<td>4</td>
<td>Severe piecemeal necrosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage</th>
<th>Fibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>1</td>
<td>Enlarged, fibrotic portal tracts</td>
</tr>
<tr>
<td>2</td>
<td>Periportal or portal-portal septa, but intact architecture</td>
</tr>
<tr>
<td>3</td>
<td>Fibrosis with architectural distortion, but no obvious cirrhosis</td>
</tr>
<tr>
<td>4</td>
<td>Probable or definite cirrhosis</td>
</tr>
</tbody>
</table>

**Lobular Activity**

- Inflammation of no necrosis
- Focal necrosis or acidophil bodies
- Severe focal cell damage
- Damage includes bridging necrosis
### APPENDIX V

**Batts & Ludwig HAI:**

<table>
<thead>
<tr>
<th>Grading Terminology</th>
<th>Descriptive</th>
<th>Lymphocytic piecemeal necrosis</th>
<th>Lobular inflammation and necrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Portal inflammatory only, no activity</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>1</td>
<td>Minimal</td>
<td>Minimal, patchy</td>
<td>Minimal; occasional spotty necrosis</td>
</tr>
<tr>
<td>2</td>
<td>Mild</td>
<td>Mild; involving some or all portal tracts</td>
<td>Mild; little hepatocellular damage</td>
</tr>
<tr>
<td>3</td>
<td>Moderate</td>
<td>Moderate; involving all portal tracts</td>
<td>Moderate; noticeable hepatocellular damage</td>
</tr>
<tr>
<td>4</td>
<td>Severe</td>
<td>Severe; may here bridging necrosis</td>
<td>Severe; prominent diffuse hepatocellular damage</td>
</tr>
</tbody>
</table>
## APPENDIX VI

### METAVIR SCORE

<table>
<thead>
<tr>
<th>1. Focal lobular necrosis</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than one necroinflammatory foci per lobule</td>
<td>0</td>
</tr>
<tr>
<td>At least one necroinflammatory foci per lobule</td>
<td>1</td>
</tr>
<tr>
<td>Several necroinflammatory foci per lobule or confluent 2 or bridging necrosis</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. Portal Inflammation</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td>Presence of mononuclear aggregates in some portal tracts</td>
<td>1</td>
</tr>
<tr>
<td>Mononuclear aggregates in all portal tracts</td>
<td>2</td>
</tr>
<tr>
<td>Large and dense mononuclear aggregates in all portal tracts</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. Piecemeal necrosis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td>Focal alteration of the periportal plate in some portal tracts</td>
<td>1</td>
</tr>
<tr>
<td>Diffuse alteration of the periportal plate in some portal tracts or focal lesions around all portal tracts</td>
<td>2</td>
</tr>
<tr>
<td>Diffuse alteration of the periportal plate in all portal tracts</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. Bridging necrosis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td>Present</td>
<td>1</td>
</tr>
</tbody>
</table>
APPENDIX VII

LIVER BIOPSY REPORT PROFORMAT PROPOSED BY SOCIETY FOR GASTROENTEROLOGY & HEPATOLOGY IN NIGERIA (SOGHIN) 2012 CONFERENCE.

Architecture

- Portal tracts
  - Number
  - Inflammation
  - Interface
  - Fibrosis
  - Bile duct
  - Ductular reaction

- Parenchyma
  - Disarray
  - Lobular inflammation
  - Apoptotic cells
  - Confluent necrosis
  - Steatosis
  - Ballooning
  - Mallory bodies
  - Kupffer cells with ceroid bodies
  - Lobular fibrosis
  - Regenerating nodules
  - Cholestasis

- Special stains
  - Iron
  - Copper-associated protein
  - Apla-1-antirypsin globules
  - HBsAg

**Comments:**

**Diagnosis:** Liver biopsy