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Risk factors of chronic liver disease amongst patients receiving care in a Gastroenterology practice in Calabar

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Abstract : *Chronic liver disease (CLD) is a common medical condition with a wide ranging etiology. Chronic hepatitis B and C viral infection are known to play key roles in the aetiology of CLD especially in sub-Saharan Africa. This study aimed to identify risk factors of chronic liver disease in Calabar.*
Methodology*: Two hundred and thirteen individuals were recruited for the study, comprising 106 patients with clinical, biochemical, ultrasonographic and histologic features of chronic liver disease and 107 apparently healthy volunteers with non-liver disease.*
Results: *The prevalence of HBsAg and Anti- HCV among the cases was 62.3% and 12.3% respectively. While among apparently healthy individuals the prevalence of HBsAg and HCV was 5.6% and 10.3% respectively. HBV infection among the cases was found to be statistically significant (p=0.001) when compared to controls.*
Conclusion: *It was concluded from this study that hepatitis B viral infection is the leading cause of CLD in patients in Calabar.*
Recommendation: *It is recommended that health advocacy strategies be implemented to enlighten the general public about the risk factors associated with CLD .This is aimed at reducing the transmission of the hepatotrophic viruses and in effect lower the burden of CLD in our environment.*
Keywords: *Calabar, Chronic liver disease, hepatitis B viral infection, risk factors*

I. Introduction

Chronic liver disease (CLD) is a major public health problem which accounts for significant morbidity and mortality figures worldwide most especially in developing countries where hepatitis B virus is also endemic [1] .The aetiology for CLD is protean and also diverse depending on the region being studied. Intravenous drug use, exposure to unhygienic traditional practices or contaminated blood products etc are established risk factors for hepatitis B and C infection [2]. Current epidemiological data reveals that in Africa and other developing countries, hepatitis B viral (HBV) infection is the most common cause of CLD, while alcohol followed by hepatitis C virus (HCV) are significant causes of CLD in developed countries of Europe and U.S.A [3,4]. Non-alcoholic fatty liver disease (NAFLD) in addition plays a major role in the aetiology of CLD particularly in areas where obesity and diabetes mellitus is a growing public health challenge.

II. Materials And Methods

2.1 , Study design; this was a cross-sectional descriptive study involving individuals with suspected liver disease referred to the gastroenterology unit of the University of Calabar Teaching Hospital (UCTH).
2.2, Eligibility criteria; these patients were aged 18 years and above. The diagnosis of chronic liver disease was made based on typical clinical, biochemical, histological and radiologic features of chronic liver disease.
2.3, Sample size estimation; sample size was calculated using the Leslie and Kish formula as follows:

$$\frac{N= z^2pq}{d^2}$$

Where:
N= the desired sample size (when population is greater than 10,000)
z= the standard deviation usually set at 1.96, which corresponds to 95% confidence interval
p= the proportion in the target population estimated to have a population characteristic i.e. 4.2% by Ansa et al [5].
q= 1.0-p
d= degree of accuracy required usually set at 0.04

$$N = \frac{(1.96)^2 \times (0.042) \times (1 - 0.042)}{(0.04)^2}$$

$$= \frac{3.8416 \times (0.042) \times (1-0.042)}{0.0016}$$

$$= \frac{0.1545706}{0.0016}$$

$$= 96.6066$$

To account for 10% non-response (attrition), the estimated minimal sample size will be 106. In order to determine the likely risk factors for chronic liver disease; age and sex matched controls of 107 individuals will be studied and the findings compared. Hence overall sample size was 213.

2.4. Sampling methods; consecutive CLD patients seen in the gastroenterology unit were recruited into the study, while consenting apparently healthy volunteers were recruited as controls.

2.5. Data collection; All patients were interviewed using a semi-structured interviewer administered questionnaire, the tool was divided into sections to include; socio-demographic characteristics, in addition seeking features suggestive of chronic liver disease (jaundice, fatigue and abdominal swelling, finger clubbing, leuconychia, wasting of the thenar/hypothenar eminence, palmer erythema, superficial distended abdominal veins). Also the presence of hepatomegaly that is firm or hard, nodular, tender or non-tender with a blunt edge or a shrunken liver was sought. In addition, 107 consenting apparently healthy Individuals, were recruited into the study as controls (i.e. 1case: 1 control). These were hospital staff and volunteers. Information about potential risk factors for viral hepatitis such as; a previous blood transfusion, intravenous drug use and abuse, past history of jaundice, major or minor surgical procedures, sharing of sharps, scarification marks, exposure to unprotected sex and/or multiple sexual partners was also sought among respondents . Further information as regards the risk factors for chronic liver disease was obtained, these included; the use of herbal concoctions, consumption of moldy grains (cooked or uncooked groundnut/ peanuts), history of diabetes mellitus (DM), smoking and alcohol consumption was also asked. Anthropometric measurements were also carried out; the height, weight, and waist circumference were measured while the body mass index (BMI) was calculated. Also respondents were tested for HBsAg and anti-HCV using enzyme linked immunosorbent assay technique (DRG ® Elisa kit, Lot no. EIA-3892 and EIA-3896 respectively). Further information obtained included results of liver function tests, serum albumin, full blood count, abdominal ultrasound scan and histological evaluation (in selected cases) of liver tissue following liver biopsy.

2.6. Data analysis; data collected was sorted out manually and then entered into the Predictive Analytics Software (PASW) version 18 IBM New York USA and subsequently analysed. Frequency tables, pie charts were used for descriptive statistics. Categorical variables was compared using the Chi-square tests. A p-value of ≤ 0.05 was considered statistically significant. Binary logistic regression was done to determine the independent risk factors of chronic liver disease. The odds ratio was used for the measure of association.

2.7. Ethical issues; ethical clearance for this study was obtained from the health research ethics committee of UCTH with health research ethics committee assigned number; UCTH/HREC/33/92.

III. Results

The age range of the cases was 18-76 years, with a mean age of 39.9 (±14.07) years. There was a male predominance (68.9%) in this study with a Male to Female ratio of 2.2: 1. Half 53 (50%) of all CLD participants were self employed. The educational level with the highest frequency of occurrence among the cases was tertiary education 46 (43.4%) followed by secondary education 38 (35.8%). Majority of the CLD patients were from the Northern (46.2%) and central (22.6%) part of Cross River State, including Bekwarra, Ishibori, Basang, Ekoi etc. TABLE 1.

A history of not receiving hepatitis B vaccination was found to be quite high (89.6%) among cases, while 54.7% and 47.2% of them admitted sharing sharps and drinking herbal medications respectively. On the other hand 46.2% admitted to having more than one sexual partner, while 31% of patients interviewed admitted receiving injection from quack doctors or nurses/scarification markings and eating moldy grains. TABLE 2.

Bivariate analysis of risk factors showed that injection received from quacks, sharing of sharps, scarification marks, consumption of herbal medications, un-protected sexual (with > 1 sexual partner) exposure, significant cigarette smoking, consumption of moldy grains and a positive family history of CLD was found to be significantly associated with CLD ($p<0.05$). TABLE 3.

Following the bivariate analysis, variables found to be significantly associated with CLD were further analyzed using binary logistic regression analysis which revealed the predictors of CLD in our environment. The risk factors found to be statistically significant were; consumption of moldy grains (p=0.001), 95% C.I = 2.854-45.288, OR = 11.37), scarification markings (p=0.050, C.I =0.805-4.414, OR= 1.886) and having more than one sexual partner (p= 0.021, C.I = 0.969- 5.186, OR = 2.242). TABLE 4.

The prevalence of HBsAg and Anti- HCV among the cases was 62.3% and 12.3% respectively. While 3.8% of the cases had HBV and HCV co-infection. HBV infection among the cases was found to be statistically significant (p=0.001) contrary to HCV infection which was not. TABLE 5.

In addition, among patients who met the criteria, the prevalence of alcoholic liver disease (ALD) and NAFLD was 14.2% and 1.9% respectively. Fig. 1.

Table 1: Socio-demographic profile of respondents

Variable	**CLD ; YES (N=106)** **Frequency (%)**	**CLD; NO (N=107)** **Frequency (%)**	**Chi-square tests**	**p-value**
Age (years)				
<20	3 (2.8)	8 (7.5)	6.402*	0.250*
20-29	23 (21.7)	31 (29.0)		
30-39	34 (32.1)	29 (27.1)		
40-49	22 (20.8)	15 (14.0)		
50-59	9 (8.5)	13 (12.1)		
≥60	15 (14.2)	11 (10.3)		
Mean	39.9± 14.07	36.8±13.96		
sex				
Male	73 (68.9)	71 (66.4)	0.154	0.695
Female	33 (31.1)	36 (33.6)		
Religion				
Christianity	105 (99.1)	104 (97.2)	-	0.621*
Islam	1 (0.9)	3 (2.8)		
Educational status				
Informal	6 (5.7)	3 (2.8)		
Primary	16 (15.1)	12 (11.2)	**10.747***	**0.012***
Secondary	38 (35.8)	22 (20.6)		
Tertiary	46 (43.4)	70 (65.4)		
Marital status				
Single	44 (41.5)	45 (42.1)	1.892*	0.759*
Currently married	60 (56.6)	59 (55.1)		
Divorced	1 (0.9)	0 (0.0)		
Widowed	1 (0.9)	3 (2.8)		
Occupation				
Student	9 (8.5)	24 (22.4)	**34.497***	**0.001***
Civil servant	24 (22.6)	31 (29.0)		
Military	5 (4.7)	3 (2.8)		
Health worker	1 (0.9)	14 (13.1)		
Self employed	53 (50.0)	33 (30.8)		
Farming	14 (13.2)	2 (1.9)		
Place of origin				
Northern CRS	49 (46.2)	24 (22.4)	**27.973**	**0.000**
Central CRS	24 (22.6)	11 (10.3)		
Southern CRS	14 (13.2)	28 (26.2)		
Others	19 (17.9)	14 (41.1)		

***Fisher's exact was used where counts are less than 5 in any cell.**

Table 2: Frequency distribution of risk factors among respondents with CLD

Variable	Frequency (106)	Percentage (%)
Injection from Quacks	33	31.1
Sharing sharps	58	24.5
Scarification marks	33	31.1
Herbal medication	50	47.2
Unprotected sexual exposure	49	46.2
***Significant cigarette smoking**	6	5.7
***** Significant alcohol consumption**	32	30.2
Moldy grains	33	31.1
Family history of CLD	14	13.2
Blood transfusion	13	12.3
Surgery	26	24.5
Female circumcision	15	14.2
No HBV immunization	95	89.6
History of Diabetes mellitus (DM)	2	1.9

***Significant alcohol consumption** = 60-80g of alcohol/day ≥ 10years for males and 20-40g alcohol/day ≥10years for females

***** **Significant cigarette smoking** = cigarette pack years ≥ 10years

Table 3: Bivariate analysis of risk factors among the respondents

Variable	CLD; YES (N=106) Frequency (%)	CLD; NO (N=106) Frequency (%)	Chi-square	p-value
Injection from Quacks				
Yes	33 (76.7)	10 (23.3)	**15.686**	**0.001**
No	73 (48.2)	97 (57.1)		
Sharing sharps				
Yes	58 (69.0)	26 (31.0)	**20.628**	**0.001**
No	48 (37.2)	81 (62.8)		
Scarification marks				
Yes	33 (70.2)	14 (29.8)	**10.086**	**0.001**
No	73 (44.0)	93 (56.0)		
Herbal medication				
Yes	50 (68.5)	23 (31.5)	**15.582**	**0.001**
No	56 (40.0)	84 (60.0)		
Unprotected sexual exposure				
≥ 1 partner	49 (76.6)	15 (23.4)	**26.280**	**0.001**
1 partner/none	57 (38.3)	92 (51.7)		
Cigarette smoking				
Significant*	6 (100.0)	0 (0)	**6.232**	**0.014**
Not significant	100 (48.3)	107 (51.7)		
Alcohol consumption				
Significant*	32 (51.6)	30 (48.4)	0.119	0.423
Not Significant	74 (49.0)	77 (51.0)		
Ingestion of Moldy grains				
Yes	33 (91.7)	3 (8.3)	**30.425**	**0.001**
No	73 (42.2)	104 (58.8)		
Family history of CLD				
Yes	14 (87.5)	2 (12.5)	**9.853**	**0.001**
No	92 (46.7)	105 (53.3)		
Blood transfusion				
Yes	13 (65.0)	7 (35.0)	2.049	0.115
No	93 (48.2)	100 (51.8)		
Surgery				
Yes	26 (57.8)	19 (42.2)	1.465	0.149
No	80 (47.6)	88 (52.4)		
Female circumcision				
Yes	15 (65.2)	8 (34.8)	2.463	0.088
No	91 (47.9)	99 (52.1)		

HBV immunization				
Yes	11 (64.7)	6 (35.3)	1.650	0.151
No	95 (48.5)	101 (51.5)		
History of DM				
Yes	2 (28.6)	5 (71.4)	1.300	0.227
No	104 (50.5)	102 (49.5)		

***Significant alcohol consumption** = 60-80g of alcohol/day ≥ 10years for males and 20-40g alcohol/day ≥10years for females

* **Significant cigarette smoking** = cigarette pack years ≥ 10years

Table 4; Logistic regression analysis showing risky practices associated with CLD in our environment.

Independent Variable	Odds ratio	95 % Confidence interval	p = value
Moldy grains			
Yes	11.37	2.85-45.288	**0.001**
No	1		
Scarification mark			
Yes	1.89	0. 805-4.414	**0.05**
No	1		
Sexual exposure			
≥ 1 partner	2.242	0.969– 5.186	**0.02**
≤ 1 partner	1		

Table 5; Comparison of prevalence of HBV and HCV infection among respondents

Variable		CLD; YES	CLD; NO	Chi-square test	p-value
HBsAg	Positive	66 (62.3)	6 (5.6)	**76.387**	**0.001**
	Negative	40 (37.7)	101 (94.4)		
Anti- HCV	Positive	13 (12.3)	11 (10.3)	0.210	0.647
	Negative	93 (87.7)	96 (89.7)		
HBV / HCV Co-infection					
	Positive	4 (3.8)	0 (0)	-	0.060*
	Negative	102 (96.2)	107 (100)		

***Fisher's exact was used where counts are less than 5 in any cell.**

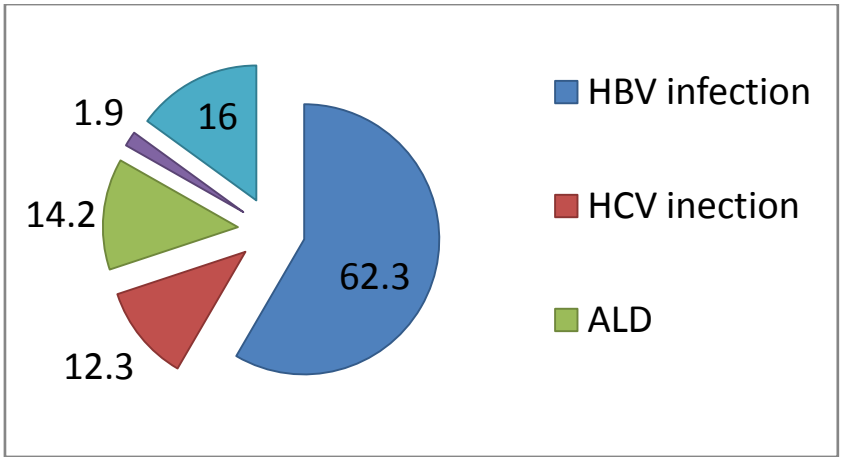

Figure 1; Summary of the aetiology of CLD

IV. Discussion

The demographic profile of the respondents revealed that greater than two-thirds of the cases were aged between 20-49 years. This is comparable with a study from Ilorin, Nigeria where it was found that most CLD patients were in the third and fourth decades of life [2]. This demographic pattern in CLD patients is common in developing countries like Nigeria [2, 6]. The involvement of a younger population in this research could be explained by the likely acquisition of hepatotrophic viruses (especially HBV) during childhood via the peri-natal or horizontal route, with development of CLD in the early decades of life [7]. More than half of the CLD patients (68.9%) were males. This finding is reflective of other studies [8, 9, 10]. The exact reason for male predominance in CLD is still unclear, though certain lifestyle habits (alcohol consumption, smoking) have been

found to be more common among the male gender placing them at increased risk of liver disease (this was yet another observation seen among cases). In addition, research has shown male predominance in HBV infection (a major risk factor for CLD), though not fully understood. Yu and his colleagues demonstrated that the male sex hormone testosterone was significantly higher in HBsAg-positive primary liver cell cancer patients when compared with controls [11].

Most (46.2%) of the cases were found among the peoples of the northern parts of Cross River State (Bekwarra being the predominant ethnic group).The finding of most cases of CLD being from the northern parts of the State is almost comparable to a study conducted in the same centre over a decade ago [5]. It is not known if unhygienic traditional risk factors for HBV are more prevalent in this region of the state accounting for the higher figures.

The independently associated risk factors for CLD (consumption of moldy grains, scarification markings and having more than one sexual partner) in this study are almost comparable to those reported by Olokoba and colleagues who had observed that the dominant ethnic group in that study indulged in harmful socio cultural practices which increased their risk of being infected by blood-borne infections such as HBV [2].They found a correlation (using Chi-square test) between liver disease and risk practices such as; consumption of native concoction, sharing blades, circumcision and scarification [2]. Furthermore he identified that irrespective of the educational status of cases there was a low level of awareness among the study population with a poor perception of the risk factors for liver disease and a misconception of not being at personal risk of liver disease [2]. This observation may possibly explain that despite the high level of education among the cases in this study they may be a similar poor perception as regards the risk factors for liver disease, though the levels of awareness of patients were not deliberately sought at the time of the study. The possible role of environmental factors such as contamination of food with aflatoxin cannot be excluded. One of the staple diets of people from the northern parts of the State is grains (groundnut, guinea corn etc). Studies have shown that food items such as grains are most likely to be contaminated by aflatoxin [12]. This may be a likely problem in these parts, due to the poor processing of grains (either by drying or storage) which invariably encourage the growth of Aspergillus flavus, the fungus which produces aflatoxin. Groundnut (a popular grain in these parts) has been found to be the most heavily contaminated food item by aflatoxin [12]. Exposure to aflatoxin increases the susceptibility to p53 mutation which is implicated in the pathogenesis of primary liver cell carcinoma (a form of CLD) [12].

It was found that the leading cause of CLD cases presenting to our facility was HBV infection with a high prevalence of 62% , this finding was found to be statistically significant (p =0.001). The implication of this result shows that HBV is by far the most important aetiologic agent of CLD in this environment and this is also in keeping with similar reports from other parts of Nigeria and the African Continent [8,10,13,14,15]. Moreover, the above findings also suggest that patients with CLD have a greater chance of being HBsAg positive, lending credence to its clinical relevance. The prevalence of HBV among CLD patients in the West African region, ranges from as high as 64% to as low as 36.7% [8, 10,14,16, 17].

Alcoholic liver disease (ALD) was the following main aetiologic agent seen among the cases with a prevalence of 14.2%. All ALD cases were both hepatitis B and C negative and were mostly men who admitted drinking > 60g of alcohol almost on a daily basis for greater than 10 years (p=0.019) and this was found to be significantly associated with ALD. This is an important finding, as it's been shown that the amount of alcohol ingested (irrespective of the type of alcohol consumed) is the most important risk factor for the development of ALD, with the risk of developing cirrhosis increasing with the ingestion of >60–80 g/day of alcohol for 10 years in men, and >20 g/day in women [18].

Hepatitis C viral infection also contributed to the aetiology of CLD among the cases with a prevalence of 12.3%, however no association with CLD was found (p=0.647). The finding in this study was similar to Lesi's work in Lagos which reported a prevalence of 12.2% among CLD patients [8]. However in that study there was a statistically significant difference between the cases and controls (p=0.009). Laraba in Maiduguri, also reported comparable findings [19]. A lack of association between HCV and CLD in this study was similar to the work done by Blankson in Ghana [14]. The relatively high HCV prevalence (10.3%) in an apparently healthy population was comparable to some other studies done in Nigeria. For instance in a population study in Keffi, Pennap et al reported a comparable prevalence of 13.3% [20]. The World health organization reports that Sub-Saharan Africa has the highest HCV prevalence rate amongst the world population [21]. In one report the prevalence of HCV was found to be 13.8% in Cameroon which shares boundary with Cross River State [22]. The proximity of Cross River State to regions of high HCV prevalence (e.g. Cameroon) may contribute to the high HCV prevalence in the state. Third generation enzyme immunoassay kits were used to detect anti-HCV (IgG) in both cases and controls, with specificity and sensitivity rates up to 99% [23] .With such a high sensitivity, confirmation with recombinant immunoblot assay is often not required [23]. Hence it may be inferred that the relatively high prevalence of HCV among apparently healthy volunteers may suggest a general increase in HCV transmission in our environment.

There is a growing interest regarding the role of NAFLD and CLD, these concerns are further heightened with the rising rate of obesity and diabetes mellitus which are known risk factors for NAFLD [24]. However, the prevalence of NAFLD was quite low (1.9%) among the cases with no significant association. None of the NAFLD cases were known diabetics, drank little (i.e. ≤ 20g alcohol/day) or no alcohol, in addition they had abnormal anthropometric measurements (obesity) and also tested negative for HBsAg and anti-HCV. Data as regards NAFLD in many parts of sub-Saharan Africa, are scarce, however, a similar prevalence rate was reported by Ndububa et al in Ife while studying the role of alcohol in CLD [25]. Among diabetics with metabolic syndrome in Lagos a higher prevalence of 8.7% was demonstrated however when compared with controls, no association was made between diabetes/ metabolic syndrome and NAFLD [26].

In sixteen percent of the CLD cases, no clear aetiologic factor could be determined. A limitation of this study was the detection of anti-HBc , anti-HBs and HBV DNA in the liver (in the setting of HBsAg loss in the presence of CLD) to determine past HBV infection. The clinical relevance of occult HBV infection (detectable HBV DNA in the liver with low level (<2000 IU/ml) or undetectable HBV DNA in blood with negative HBsAg status), with or without serological markers of previous exposure (anti-HBs and or anti-HBc) is uncertain in this study [27]. Current reports suggest that occult hepatitis B viral infection (OBI) may be associated with ongoing chronic hepatitis, liver fibrosis and subsequent development of hepatocellular cancer [28]. Furthermore, it's been found that the prevalence of OBI is associated with the overall prevalence of HBV infection in a given country [28]. Consequently individuals from countries highly endemic for HBV (e.g. sub-Saharan Africa) are more likely to have OBI [28]. Based on this premise, the role of OBI infection was not fully excluded in our CLD patients as it was beyond the scope of this study. Although an emerging area of research in our environment, the role of OBI in CLD in Nigeria cannot be downplayed.

Despite the role hepatotrophic viruses (HBV and HCV), significant alcohol consumption and NAFLD played in the aetiology of CLD in this study, other causes of CLD such as hereditary metabolic diseases (Hereditary haemochromatosis, Wilsons disease, α1- Antitrypsin Deficiency etc), autoimmune liver disease (autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis), parasitic / fungal infestations of the liver etcetera could not be excluded at the time of this study. Some forms of CLD (e.g. hereditary metabolic diseases) are often found in the northern hemisphere [29, 30]. The role of autoimmune/ cholestatic / metabolic liver disease in Africa is yet to be fully elucidated, probably due to its rarity amongst Africans or lack of accessibility to diagnostic tools.

V. Conclusion

The conclusions derived from this study revealed that there was a major association between HBV infection and significant consumption of alcohol with CLD. In addition common practices related to risk factors of CLD include; history of scarification marks, having more than one sexual partner and consumption of moldy grains.

Therefore it is recommended from this study that public health strategies be advocated to encourage safe sex practices (abstinence /use of condoms), universal HBV vaccination as well as discouragement of traditional practices such as female circumcision and scarification markings. All these measure are in a bid to reduce the transmission of HBV and HCV infections and their consequent sequelae. The general public should also be enlightened about the deleterious effect of alcohol on the liver especially when consumed in significant amounts. It is hoped that this study will stimulate further research regarding the role of other aetiologic agents of CLD (such as metabolic , autoimmune liver disease etc) and also the contribution of occult hepatitis B viral infection and aflatoxin (from moldy grains) in CLD in our environment.

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References

[1]. M J Mphahlele , G Francis , M C Kew , P Van Damme , Epidemiology and control of Hepatitis B: Implications for Eastern and Southern Africa. The South African Journal of Epidemiology and Infection, 17 (1,2) , 2002 , 12-17.
[2]. A B Olokoba, S A Aderibigbe , O O Kayode , A community survey of practices related to risk factors for liver diseases among adults in Ilorin metropolis Am. J. Sci. Ind. Res., 1(2), 2010, 118-121.
[3]. B J Bojuwoye , The burden of viral hepatitis in Africa. West Afr J Med, 16(4), 1997, 198-203.
[4]. Z M Younossi , M Stepanova , M Afendy , Y Fang , Y Younossi , H Mir , et al , Changes in the prevalence of the most common causes of chronic liver diseases in the United States from 1988 to 2008. Clin Gastroenterol Hepatol, 9(6), 2011, 524-530.
[5]. V O Ansa , E J Peters , J U Ekott , Distribution of liver diseases among medical admissions in University of Calabar teaching hospital. Mary Slessor journal of medicine, 2 (2), 2000, 6-9.
[6]. E N Okeke , C A Daniyam , M Akanbi , S O Ugoya , E I Agaba , Lipid Profile of Patients with Liver Cirrhosis in Jos, Nigeria Journal of Medicine in the Tropics, 12, 2010, 56-59.
[7]. R Perrillo. Hepatitis B and D (Sleisenger and Fordtran's gastrointestinal and liver disease: Pathophysiology, diagnosis, management. Vol. II, 9th ed. Philadelphia: Edited by Mark Feldman, Lawrence S. Friedman, Lawrence J. Brandt, 2010, 1287-1311).

[8]. O A Lesi , M O Kehinde , E E Anomneze, Chronic liver disease in Lagos: A clinic-pathological study. Niger Postgrad Med J. 11(2), 2004 , 91-6.
[9]. S C Nwokediuko , P C Osuala , U V Uduma , A K Alaneme , C C Onwuka , C Mesigo , Pattern of liver disease admissions in a Nigerian tertiary hospital. Nigerian Journal of Clinical Practice, 16 (3) , 2013, 339-341.
[10]. U C Okonkwo , Mortality from chronic liver disease in Anambra State- A study of the predictive ability of selected indices, Child-Pugh and MELD scores, National Post Graduate Medical College of Nigeria disss., Badagry, Lagos, 2005.
[11]. M Yu , S Yang, S Cheng, Y Liaw , S Lin , C Chen , Hormonal Markers and Hepatitis B Virus-Related Hepatocellular Carcinoma Risk: a Nested Case–Control Study Among Men. Journal of National cancer institute, 93 (21), 2001.
[12]. R Igetei , J Otegbayo , D A Ndububa , O A Lesi , C I Anumudu , P Hainaut et al, Detection of p53 codon 249 mutation in Nigerian patients with hepatocellular carcinoma using a novel evaluation of cell-free DNA. Annals of Hepatology, 7(4), 2008, 339-344.
[13]. A A Otu , Hepatocellular carcinoma, hepatic cirrhosis, and hepatitis B virus infection in Nigeria. Cancer, 15, 60 (10), 1987, 2581-5.
[14]. A Blankson , E K Wiredu , R K Gyasi , A Adjei, Y Tetty , Sero-prevalence of Hepatitis B and C viruses in Cirrhosis of the Liver in Accra, Ghana. Ghana Medical Journal, 39 (4), 2005, 132-137.
[15]. A G Ayele , S Gebre-Selassie , Prevalence and Risk Factors of Hepatitis B and Hepatitis C Virus Infections among Patients with Chronic Liver Diseases in Public Hospitals in Addis Ababa, Ethiopia. Tropical Medicine, (2013), 2012, 1-7.
[16]. G Fattovich, Natural history of hepatitis B. Journal of Hepatology, 48 (2), 2008, 335-352.
[17]. C Madubuike , The prevalence of acute HDV super-infection in HBsAg-positive chronic liver disease patients at the University of Port Harcourt Teaching Hospital, West African College of Physicians diss., 2009.
[18]. R O'Shea, D Srinivasan , M J Arthur , Alcoholic liver disease. Am J Gastroenterol, 105, 2010, 14–32.
[19]. A Laraba , G Wadzali , B Sunday , O AbdulfataI , S Fatai , Hepatitis C Virus Infection In Nigerians With Chronic Liver Disease. The Internet Journal of Gastroenterology, 9 (1) , 2010, 1528-8323.
[20]. G R Pennap , A Yakubu , O Oyige O, J Forbi, Prevalence of hepatitis B and C virus infection among people of a local community in Keffi, Nigeria. African Journal of Microbiology Research, 4 (4), 2010, 274-278.
[21]. V Madhava , C Burgess , E Drucker , Epidemiology of chronic hepatitis C virus infection in sub-Saharan Africa. The Lancet Infectious Diseases, (2) ,2002 , 293-302.
[22]. C Laurent , A Bourgeois ,M Mpoudi ,C Butel, E Mpoudi-Ngolé , E Delaporte , HIV and Hepatitis C Virus Co-infection, Cameroon. Emerging Infectious Diseases, (13), 2007, 515-512.
[23]. J G O'Leary, G L Davis G L, Hepatitis C (Sleisenger and Fordtran's gastrointestinal and liver disease: Pathophysiology, diagnosis, management. Vol. II, 9th ed. Philadelphia, Edited by Mark Feldman, Lawrence S. Friedman, Lawrence J. Brandt, 2010, 1313-1327).
[24]. A E Reid , Nonalcoholic Fatty Liver disease (Sleisenger and Fordtran's gastrointestinal and liver disease: Pathophysiology, diagnosis, management. Vol. II, 9th ed. Philadelphia, Edited by Mark Feldman, Lawrence S. Friedman, Lawrence J. Brandt. ,2010, 1401-1408).
[25]. D A Ndububa , O S Ojo , V A Adetiloye , O Adekanle, The contribution of alcohol to chronic liver disease in patients from South-West Nigeria. Nigerian Journal of clinical practice, (13), 2010, 360-364.
[26]. C Onyekwere , A Ogbera , B O Balogun , Non- alcoholic fatty liver disease and the metabolic syndrome in an urban hospital serving an African community. Ann Hepatol, 10 (2), 2011, 119-24.
[27]. EASL Clinical Practice Guidelines, Management of chronic hepatitis B virus infection, Journal of Hepatology, (57), 2012, 167–185.
[28]. H Nishikawa , Y Osaki , Clinical Significance of Occult Hepatitis B Infection in Progression of Liver Disease and Carcinogenesis, Journal of Cancer, (4) 2013, 473-480.
[29]. E Kaner , D Newbury-Birch , L Avery , K A Jackson , A rapid review of liver disease epidemiology, treatment and service provision in England: By the Institute of Health and Society, Newcastle, funded by the Department of Health, Policy Research Programme (grant reference LVR/012), 2007.
[30]. R W Kim , R S Brown , N Terrault , H El-serag , Burden if liver disease in the United states: Summary of a workshop, Mayo Clinic and Foundation, Rochester, MN, 2012.