CLINICAL PRESENTATION AND MAGNITUDE OF HEPATITIS B INFECTION AMONG PATIENTS WITH LIVER CIRRHOSIS ATTENDING MUHIMBILI NATIONAL HOSPITAL.

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By

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A dissertation submitted in partial fulfillment of the Requirements for the Degree of Masters of Medicine (Internal Medicine) of the Muhimbili University of Health and Allied Sciences

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CERTIFICATION

The undersigned certify that he has read and hereby recommends for acceptance by the Muhimbili University of Health and Allied Sciences a dissertation entitled "*clinical presentation and magnitude of hepatitis B infection among patients with liver cirrhosis attending Muhimbili National Hospital"* in partial fulfillment of the requirements for the degree of masters of medicine in Internal Medicine Muhimbili University of Health and Allied Sciences.

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Dr. Ewaldo Komba

(Supervisor)

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Date

DECLARATION AND COPYRIGHT

I, **Wolfgang Bernard Shirima**, Declare that this dissertation is my own original work and that it has not been presented and will not be presented to any other University for a similar or any other degree award.

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DEDICATION

To my family for its sacrifice, My wife Dr. Judith Cosmas for her kindness and everlasting support despite being a mother and a resident student.

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ABBREVIATIONS

AIH	-	Autoimune Hepatitis
ALD	-	Alcoholic liver Disease
ALT	-	Alanine Aminotransferace
ASAT	-	Aspartate Amino transferase
CP	-	Child Pugh
DNA	-	Deoxy Ribonucleic Acid
FBP	-	Full Blood Picture
HBsAg	-	- Hepatitis B surface Antigen
HBV	-	Hepatitis B Virus
HCC	-	Hepatoccelular Carcinoma
HCV	-	Hepatitis C Virus
HE	-	Hepatic Encephalopathy
HPS	-	Hepatopulmonary Syndrome
HRS	-	Hepatorinal Syndrome
HSC	-	Hepatic Stellate Cell
INR	-	International Norrmalization Ratio
LL	-	Lower Limb
LN	-	Lymph Node

MELD	-	Model for End stage Liver Disease
MNH	-	Muhimbili National Hospital
MUHAS	-	Muhimblili University of Health and Allied Science.
NAFLD	-	Non Alcoholic Fatty liver Disease
PBC	-	Primary Biliary Cirrhosis
PSC	-	Primary Sclerosing Colangitis
PT	-	Prothrombin Time
PTT	-	Partial Thromboplastine Time
RAAS	-	Renine Angiotensine Aldosteron System
TIPS	-	Transjugular Intrahepatic Porto systemic Shunt
USS	-	Ultrasound
WHO	-	World Health Organization
WHVP	-	Wedge Hepatic Venous Pressure

ABSTRACT

Background

Chronic liver disease is responsible for over 1.4 million deaths annually. In the western world this disease is among the top ten of disease-related causes of death. The World Health Organization (WHO) estimates that in 2002 liver cirrhosis and primary liver cancer caused 783,000 and 619,000 deaths, respectively. Taken together, these conditions represented approximately one of every forty deaths (2.5%) worldwide. In Tanzania liver cirrhosis is one of the leading diseases among the liver disorders. Although major causes of liver cirrhosis varies in different regions of the world, but overall hepatitis B virus remain the commonest cause of liver cirrhosis worldwide.

In Tanzania very little has been published on liver cirrhosis and no studies done regarding clinical presentation and the magnitude of HBV infection among patients with liver cirrhosis. Scarcity of information on the extent of this problem in our set up may halt the effort to prevent, timely diagnose and give better care to our patients with liver cirrhosis.

Objective

The main objective of this study was to describe the clinical presentations and determine the magnitude of Hepatitis B viral infection among patients with liver cirrhosis attended Muhimbili National Hospital Tanzania (MNH).

Methods

The study design was hospital based descriptive study, which was conducted in the surgical and medical Gastroenterology units, starting from July 2012 to February 2013.

Results

Out of the 81 liver cirrhotic patients 60(74%) were males.

Ascites (92%) was the commonest clininical presentation, followed by lower limb edema (56%). Other stigmatas of chronic liver disease such as dupyutrens contracture, spider naevi and caput medusa were seen in minority of patients.

Prevalence of HBsAg was found to be 48% among patients with liver cirrhosis.

Large proportion of patients had MELD score of 19 and below.

Conclusion: Liver cirrhosis is more common in males. Mean age of patients with liver cirrhosis in this study is 39±14.582 years. Prevalence of HBsAg among patients with liver cirrhosis in this study is high (48%). Majority of patients with liver cirrhosis in this study present to the hospital with very advanced decompensated liver cirrhosis. Large proportion (84%) of patients with liver cirrhosis in this study had low MELD score.

CHAPTER ONE

1.0. INTRODUCTION AND LITERATURE REVIEW

1.1. LIVER CIRRHOSIS

1.1.1. Definition of liver cirrhosis:

Liver cirrhosis is defined as the end stage of chronic damage to the liver which is characterized by fibrosis resulting in to distortion and destruction of normal liver architecture. Functional liver tissue is destroyed and replaced by regenerating nodules that do not fully restore lost liver function.[1]

Thus unique to the liver and its cirrhotic stage is the occurrence of septal fibrosis, including portal–central septa carrying shunting vessels, and nodular parenchymal regeneration resulting in distorted architecture.[1]

1.1.2. Causes of liver cirrhosis:

The main causes of cirrhosis are: alcoholic liver disease (ALD), hepatitis B (HBV), hepatitis C (HCV), non-alcoholic steatohepatitis (NASH), haemochromatosis, auto-immune hepatitis (AIH), primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) [2]

Causes of liver cirrhosis varies worldwide.Whereas in Europe and North America high alcohol consumption is a very frequent cause of cirrhosis of the liver, in many Asian and Africans countries hepatitis B virus is the most important etiological agent.[3, 4]

A study done by Abdelsalam Mohamed in sudan regarding aetiology and complications of liver cirrhosis alcohol consuption was found to be the commonest cause of liver cirrhosis followed by hepatitis B virus infection[5]

The etiology of liver cirrhosis in Europe and America is predominately chronic alcohol consumption and infection with hepatitis C virus[3,4] Weither the total amount of alcohol

ingested over time or other factors, such as genetic factors, type of alcoholic beverage ingested, and drinking patterns play a significant role in causing chronic liver damage is not completely clear[11] However a studies done in different parts of Europe has found that increasing alcohol above 30g/day is associated with increase in risk of liver damage[6,7]

Patients with hepatitis infection and who take alcohol are at increased risk of developing liver diseases. In a case control study done by Thomas R. et al in USA regarding the role of alcohol and viral hepatitis on chronic liver disease found that, alcohol and hepatitis virus have synergistic effect on causing chronic liver disease [8]

Another important cause of liver cirrhosis is non- alcoholic fatty liver disease. Non-alcoholic fatty liver disease (NAFLD) is a common condition characterised by excess of fat in liver which ranges from simple steatosis to steatohepatitis, cirrhosis and hepatocellular carcinoma (HCC) in the absence of excessive alcohol intake. Metabolic syndrome and conditions associated with it like diabetes, obesity and dyslipidemia are predisposing factors of NAFLD [9]. NAFLD is becoming a major public health problem due to rising incidence of obesity and type II diabetes. Its prevalence is 15-40% in western countries and 9-40% in Asian countries.[9] Pathogenic process leading to fibrosis and cirrhosis in NAFLD, include mitochondria injury, stellate cell activation and microvasculal injury through profibrogenic cytokines liberated in response to hyperglycaemia or necroimflamatory changes. Adams L.A et al notted that patients with NAFLD have up to 60% projected rate of developing liver complications including liver cirrhosis[10]

1.1.3. Epidemiology of liver cirrhosis

The exact prevalence of cirrhosis worldwide is unknown. It is estimated that the prevalence of liver cirrhosis is 0.15% or 400,000 in the USA where it accounted for more than 25,000 deaths and 373,000 hospital discharges in 1998[11,12] Similar numbers have been reported from Europe, and numbers are even higher in most Asian and African countries where chronic viral hepatitis B and C are frequent.

Prevalence of liver cirrhosis is increasing worldwide, This increase in prevalence may reflect the increase in the society of several risk factors for liver cirrhosis such as chronic alcohol consumption, Non Alcoholic Fat Liver Disease, obesity and type 2 diabetes [13]

In a cohort study done by kanwal F, et al in USA found the double increase in prevalence of liver cirrhosis from 9% in 1996 to 18.5% in 2006[14] In a retrospective study done in UK by Fleming KM et al found that there was a 45% increase in the incidence of cirrhosis during the decade 1992–2001 in the UK and a 68% increase in prevalence [15]

In another epidemiological study done by Fleming CM in UK in 2010 also showed an increasing trend in both incidence and prevalence of liver cirrhosis, with an estimated 45% increase in incidence in the period of 10 years.[13]

In Tanzania liver cirrhosis rank the second among the spectrum of disorders that affect liver. In a prospective study regarding the etiology of liver diseases done by Stahel et al in rural Tanzania, they found that liver cirrhosis contributed to 31% of the liver diseases, this being the second disorder after bacteria and protozoa which contributed in 33%. Liver neoplasm's was found in 21% of all the liver disorders [16]

1.1.4. Clinical features and complications of liver cirrhosis.

Many chronic liver diseases are characterized by a slow and indolent Course with non-specific clinical presentation and this may lead to a later diagnosis. Cirrhosis is frequently indolent, asymptomatic and unsuspected until complications of liver disease are present. A substantial proportion of these patients never come to clinical attention, and previously undiagnosed cirrhosis is still frequently found at autopsy [17] Initially patients may experience fatigue, weakness, and exhaustion. Loss of appetite is usual, often with nausea and weight loss. Unfortunately most patients with liver cirrhosis come late to hospital with very advanced decompensated liver cirrhosis[18] Therefore initial clinical presentation of patients with decompensated cirrhosis is still comon and is characterized by the presence of dramatic and life-threatening complications, such as

variceal hemorrhage, ascites, spontaneous bacterial peritonitis, or hepatic encephalopathy[19]

A new scheme for the analysis of the natural history of cirrhosis and the identification of prognostic factors was proposed and agreed upon the International Consensus Workshop of Baveno IV [2]. The scheme identifies four clinical stages of cirrhosis: stage 1 which is characterized by the absence of esophageal varices and of ascites; stage 2 which is characterized by the presence of esophageal varices without ascites and without bleeding. The development of ascites, with or without varices, in a patient who has never bled is the hallmark of stage 3. Gastrointestinal bleeding with or without ascites characterizes stage 4. Cirrhosis is defined as compensated when the patient is in stages 1 and 2, decompensated in stages 3 and 4.

To assess the severity of the liver disease, scoring models have been used.The oldest model is the Child-Pugh (CP) classification[20] The CP classification is based on bilirubin level, prothrombin time, albumin and the presence and/or severity of ascites and encephalopathy (Table below)

The child pugh classification

Points	1	2	3
Encephalopathy grade	None	1&2	3&4
Ascites	Absent	Slight	Moderate
S.bilirubin(mmol/l)	<35	35-50	>50
S.albumin(g/l)	>35	28-35	<28
INR	<1.3	1.3-1.8	>1.8

The points for all five parameters involved are summed up and patients classified into one of the three classes A, B or C. class A 5-6 points, class B 7-9 points and class C >10 points.

One of the drawbacks of the CP classification is subjective assessment (encephalopathy and ascites) and another model has been developed for the assessment of prognosis which is the Model of End-stage Liver Disease (MELD) [21] In this model there are only objective parameters, bilirubin, prothrombin time and creatinine. It has been shown to be reliable to estimate mortality risk for patients with end-stage liver disease of various etiologies [22] MELD uses three laboratory values to predict survival, It is calculated according to the following formula:

MELD = 3.78[Ln serum bilirubin (mg/dL)] + 11.2[Ln INR] + 9.57[Ln serum creatinine (mg/dL)] + 6.43

MELD score	3 month mortality
40 or more	71.3% mortality
30–39	52.6% mortality
20–29	19.6% mortality
10–19	6.0% mortality
<9	1.9% mortality

Patients with MELD scores 17 or greater are considered candidates for liver transplantation. Patients with scores <15 are deferred.

The development of jaundice, ascites, hepatic encephalopathy (HE) or bleeding oesophageal varices signals decompensation [23]

Ascites

Ascites is the most common major complication of cirrhosis and is an important landmark in the natural history of chronic liver disease. If observed for 10 years, approximately 60% of patients with cirrhosis develop ascites requiring therapy [24, 25]

Ascites is defined as the accumulation of fluid in the peritoneal cavity. It is a common clinical finding, with various extraperitoneal and peritoneal causes but it is most often results from liver cirrhosis. Onset of ascites in cirrhosis of the liver is associated with worsened quality of life, increased risk of spontaneous bacterial peritonitis, and renal failure. The development of ascites in a cirrhotic patient generally heralds deterioration in clinical status and portends a poor prognosis [25] Treatment of ascites involves use of low sodium diet, use of deuretics, Large volume paracentesis and use of TIPS. [26]

Variceal Hemorrhage

Varices are dilated submucosal veins, although varices may form in any location along the tubular gastrointestinal tract, they most often appear in the distal few centimeters of the esophagus.[27] Varices are the portosystemic collaterals that form after pre-existing vascular channels are dilated by portal hypertension. Dilation generally is clinically significant once the wedged hepatic venous pressure (WHVP) gradient is elevated above 12 mm Hg (normal, <5 mm Hg). The WHVP is defined as the gradient between the wedged hepatic venous pressure and the free hepatic venous pressure measured by a catheter threaded down through the jugular vein [27].

Approximately 50% of patients with cirrhosis develop gastroesophageal varices. Clinical and endoscopic predictors of a first variceal hemorrhage include advanced Child-Pugh score, continued alcohol use, large varices, and presence of red wale markings. [28]

Bleeding

Patients with liver cirrhosis as in other end stage liver diseases may present with signs and symptoms of bleeding tendency. Bleeding in liver cirrhosis is caused by decreased levels of most procoagulant factors, with the notable exceptions of factor VIII and von Willebrand factor, which are elevated[29] The decrease in procoagulant factors is primarily due to decrease in synthetic ability of the diseased liver. Bleeding can also be due to thrombocytopenia. Thrombocytopenia is a common complication in patients with chronic liver disease that has been observed in up to 76% of patients [30] Multiple factors can contribute to the development of thrombocytopenia in liver cirrhosis, including

splenic platelet sequestration, bone marrow suppression by chronic hepatitis C infection, and antiviral treatment with interferon-based therapy. Reductions in the level or activity of the hematopoietic growth factor thrombopoietin may also play a role. [30]

Another common complication of liver cirrhosis is hepatocellular carcinoma. Majority of patients with liver cirrhosis will complicate to malignant transformation ending into development of hepatocellular carcinoma (HCC).[31] Kato Y.et al reported that cirrhosis precedes most cases of hepatocellular carcinoma and that 70%–90% of HCC develop from a background of chronic liver cirrhosis or inflammation. These data clearly indicate the critical importance of early diagnosis of hepatic cirrhosis. The main mechanism for liver cirrhosis to predispose individuals to HCC might be through the chronic necroinflammation and regenerative proliferation. Studies have shown that the mortality rate of HCC associated with cirrhosis is rising in some developed countries, whereas mortality from non-HCC complications of cirrhosis is decreasing or is stable [31]

Liver cirrhosis is regarded as the most important premalignant lesion of HCC. It is reported that yearly incidence of HCC among patients with clinical liver cirrhosis ranges from 3 to 11 percent. [32] In a prospective study done by Ming-Whei Yu et al in Taiwan to determine the incidence of hepatocellular carcinoma and liver cirrhosis among asymptomatic chronic hepatitis b carriers found that, the relative risk of developing HCC among patients with liver cirrhosis to be 12 times those without liver cirrhosis. [33]

Hepatic encephalopathy

Hepatic encephalopathy (HE) is defined as mental or neuromotor dysfunction in a patient with acute or chronic liver disease. [34] HE develops slowly in cirrhotic patients, starting with altered sleep patterns and eventually progressing through asterixis to stupor and coma. The acute form of HE is often associated with fulminant hepatic failure and can rapidly progress to seizures, coma, and death. [34]

In patients with cirrhosis, acute encephalopathy is most commonly associated with a precipitating factor, such as electrolyte disturbance, medications, gastrointestinal hemorrhage, or infection. Recurrent HE can occur with or without a precipitating factor

and is usually easily reversible. Persistent HE is rare and is defined as the persistence of neuropsychiatric symptoms despite aggressive medical and dietary therapy. The most common form of HE is not always clinically apparent: A patient with subclinical HE has only mild cognitive deficits or subtle personality changes. [17] Prevention and treatment of HE in cirrhotic patients continues to rely on ammonia-lowering strategies which include assessment of dietary protein intake and the use of lactulose, neomycin, sodium benzoate and L-ornithine-aspartate [17]

Hepatorenal syndrome

Hepatorenal syndrome (HRS) is another complication of liver cirrhosis. The term hepato-renal syndrome describes a functional kidney failure in patients with end-stage liver disease. In cirrhotic patients, hepato-renal syndrome is a frequent complication affecting up to 40% of this population [35, 36] Pathogenesis of HRS involves two mechanisms; the first one is intense arterial vasodilation in the splanchnic vasculature, resulting in the pooling of blood in this area. The vasodilation is thought to be mediated mainly by nitric oxide but other mediators such as prostacyclin and other prostaglandins may also contribute [37]. Secondly, advanced liver disease is associated with a progressive reduction of cardiac output caused by cirrhotic cardiomyopathy. The result is a hyperdynamic circulation with ineffective circulating blood volume. In order to increase effective circulating blood volume, systemic vasoconstrictor systems such as the renin–angiotensin–aldosterone system and the sympathetic nervous system are activated. The consequences are increased retention of sodium and water and decreased renal perfusion leading to functional renal impairment. [38]

Patients with liver cirrhosis develop progressive circulatory dysfunction, which induces activation of the renin-angiotensin-aldosterone system (RAAS), activation of the sympathetic nervous system and increased activity of antidiuretic hormone. Such activation results in renal fluid retention, ascites and dilutional hyponatremia[39]

Hepatopulmonary syndrome

Hepatopulmonary syndrome (HPS) is one of the complications among patients with liver cirrhosis. It is associated with shortened patient survival before and after liver transplantation [40] HPS is defined as a triad, represented by intrapulmonary vascular dilatation (IPVD) associated with an alveolar-arterial oxygen tension difference (A-aDO_2) $\geq$ 15 mmHg or a PaO_2 < 80 mmHg and liver disease[41]

Prevalence of HPS among patients with liver cirrhosis varies based on severity of cirrhosis, age of patients and diagnostic tool for HPS. In a study done by Peter Deibert et al regarding HPS in patients with liver cirrhosis and the role of pulse oxymetry, they found a prevalence of HPS among patient with liver cirrhosis to be 1.3%. They also found that patients with HPS were younger than those without HPS and cirrhosis [42]

1.2. Pathophysiology of liver cirrhosis:

Liver cirrhosis is an advanced stage of liver fibrosis that resulted from chronic damage to the liver [43] Liver fibrosis, or scarring, occurs as an attempt to limit tissue damage in response to chronic liver injury, regardless of the etiology. It is characterized by excessive deposition of extracellular matrix proteins, especially alpha 1 collagen [44] Fibrosis progresses at variable rates depending on the cause of liver disease, environmental factors and host factors.[45] Liver cirrhosis is accompanied by distortion of the hepatic vasculature leading to shunting of the portal and arterial blood supply directly into the hepatic outflow (central veins), compromising exchange between hepatic sinusoids and the adjacent liver parenchyma, i.e., hepatocytes.

The hepatic sinusoids are lined by fenestrated endothelia which rest on a sheet of permeable connective tissue (the space of Disse) which contains hepatic stellate cells (HSC) and some mononuclear cells. The other side of the space of Disse is lined by hepatocytes which execute most of the known liver functions. In cirrhosis the space of Disse is filled with scar tissue and endothelial fenestrations are lost, a process termed sinusoidal capillarization[46]

1.3. Prevalence of hepatitis B Virus and its transmission

Hepatitis B virus is one of the most common infectious diseases in the world. Over 2 billion individuals are infected by hepatitis B virus (HBV) globally and over 350 million are chronically infected with chronic infection manifested by persistence of the virus and HBV surface antigen (HBsAg) in serum and production of viral antigens and HBV DNA in the liver [47]

The prevalence of chronic hepatitis B virus infection varies by geographic region. In European countries prevalence of HBsAg is very low ranging between 1%-2%[48] In Africa it is estimated that 50 million people are chronic carriers of hepatitis B virus and that in subsaharan Africa carrier rates range from 9% to 20% [49].

In Tanzania prevalence of hepatitis B virus is high. In a seroprevalence study done by Shao et al in Dares salaam Tanzania found that prevalence of all markers of HBV was 70.7%. But the prevalence of hepatitis B surface antigen was positive in 6% of all subjects. [50] In another study done in mwanza Tanzania by Jacobs et al found the prevalence of HBsAg to be 9.9% [51]

1.3.1. Natural history of HBV

The incubation period of HBV following infection is 40-150 days, with an average of approximately 12 weeks. Following infection the individual will go through the incubation, prodromal and convalescence periods with various viral markers appearing in blood [52]

The natural history of HBV infection is complex and variable and is greatly influenced by the age at infection, the level of HBV replication, and host immune status. The progression to chronic HBV infection characteristically starts with an acute infection, indicated by the presence of HBsAg. Serum tests for HBsAg remain positive as long as chronic infection is present. Positivity for HBeAg, a marker of higher viral load and heightened infectivity, also develops, and may remain for months to years. Resolution of infection is heralded by disappearance of HBsAg. In this case, the anti-HBc and anti-

HBs are positive. [53] Chronic HBV usually causes microinflamatory changes that evoke a fibrotic response in the liver, and many infected individuals will eventually develop cirrhosis. Inactive HBsAg carriers often bypass the development of cirrhosis but remain at risk for HCC if their viral load is very high. This is particularly true when infection is acquired in infancy.[53]

1.3.2. Transmission of Hepatitis B virus.

Hepatitis B virus is mainly transmitted by parenteral route The parenteral transmission includes injection drug use, transfusions and dialysis, acupuncture, working in a health-care setting, tattooing and household contact. In the United States and Western Europe, injection drug use remains a very important mode of HBV transmission (23% of all patients**)** [54]

In Asia the region most affected by hepatitis B infection the virus is transmitted primarily in the perinatal period. In Africa transmission occurs predominantly in early childhood rather than at birth. The mechanisms of transmission during childhood remain uncertain. In Western countries, HBV is predominantly a disease of adolescents and adults as a result of high risk sexual behavior or injection drug use [54]

The age at acquisition of HBV has a large impact on the likelihood of the disease becoming chronic. The chance of chronic infection is 90% or greater among neonates who become infected with HBV through perinatal transmission. Exposure during adolescence or young adulthood is associated with a 95% or greater likelihood that the disease will be self-limiting. [55]

In their study Blankson et al found that HbsAg positive patients with liver cirrhosis were in the age range between 20-49years indicating that HBV was acquired during childhood through to early adulthood. [55]

1.4.0. Liver cirrhosis and hepatitis B infection.

Hepatitis B virus is one of the most common infectious diseases in the world. Over 2 billion individuals are infected by hepatitis B virus (HBV) globally and approximately 350 million people over 5% of the world's population are chronic carriers of the hepatitis B virus (HBV), of whom it is estimated that 25-30% will die of the sequelae of their infection, principally cirrhosis and hepatocellular carcinoma. This is equivalent to over a million human dearths annually of HBV-related chronic liver disease. [56]

The mean age of onset of cirrhosis in chronic HBV infection acquired during childhood, is about 40 years and complications become clinically evident 3 to 5 years later. It is estimated that the annual rate of hepatic decompensation is 4% in cirrhotic patients with viraemia and 1% in those without viraemia [57]

Prevalence of HBV infection among patients with liver cirrhosis varies by geographical region. The burden of chronic carriage falls predominantly in Asia where 75% of chronic HBV carriers live. Africa has the second largest number of chronic carriers. Of approximately 470 million people living in Africa, about 50 million are lifetime carriers of the virus and as many as 12.5 million will eventually die due to hepatitis B induced liver disease. This represents a risk of 25% among chronic carriers. [49]

A cross section study done by Alexandra et al regarding prevalence of HBV infection among patients with chronic liver disease in Asian countries found that 71% to 80% of patients with chronic liver disease were HBsAg positive [58] In their study they found that 30% of patients with liver cirrhosis in Thailand were positive for HBsAg, with similar number also observed in Taiwan. However in china they found that 78% of patients with liver cirrhosis were HBsAg positive.

In a study done by Blankson et al in Ghana regarding seroprevalence of HBV and HCV omong patients with liver cirrhosis, they found a prevalence of hepatitis B virus to be 42.9% [55]

In kenya Okoth F. et al in their study regarding the privalence of hepatitis B carriers among patients with liver cirrhosis and hepatocellular carcinoma found the prevalency of HBsAg positivity to be 15.4% among liver cirrhosis patients.[59] In another similar study also done in Kenya found the prevalence of HBsAg to be 25% among liver cirrhosis and 33% among HCC patients[60]

In a study done by Molyneux ME in Malawi the prevalence of HBsAg was found to be 54.8% among patients with liver cirrhosis [61]

1:5 Treatment of liver cirrhosis.

Following chronic liver injury of any etiology, there is progressive fibrosis, which if persistent leads to cirrhosis and liver failure. Detailed analysis of the cellular and molecular mechanisms that mediate liver fibrosis has provided a framework for therapeutic approaches to prevent, slow down or even reverse fibrosis and cirrhosis. [62] Despite this advances, to date no specific drugs made available to stop or reverse liver fibrosis or cirrhosis. Removing the causative agent is the only effective therapy to stop or even reverse liver fibrosis [62]

Therefore treatment strategies for liver fibrosis may vary on an individual basis according to etiology, risk of fibrosis progression and the prevailing pathogenic milieu, meaning that a multi-agent approach could be required. For alcoholic liver cirrhosis abstinence from alcohol remains the single most important factor that determines long term survival. Abstaining from alcohol has shown to stop further progression of liver injury and hence prolonging life. [63]

Studies have shown that even for non alcoholic cirrhosis like hepatitis induced cirrhosis continuing alcohol consumption plays a major role in the deterioration of virus related chronic liver disease and its progression to hepatocellular carcinoma.[64]

1:6 Treatment of hepatitis B virus among liver cirrhosis patients.

In patients with compensated hepatitis B virus (HBV) cirrhosis, active viral replication correlates significantly with the risk of hepatic flare, decompensation, and the

development of hepatocellular carcinoma (HCC). The 5-year survival of patients with compensated cirrhosis was reported to be 80 to 85%, and is significantly lower in patients with replicative HBV [65] Suppression of HBV replication has therefore resulted in reduction of hepatic necroinflammation and improvement of liver function in patients with liver cirrhosis. [65] Early treatment should be instituted because once decompensation occurs, mortality increases remarkably.

Interferon-Alpha

Interferon-alpha or its pegylated version is safe and effective in patients with chronic hepatitis B and in selected patients with compensated HBV cirrhosis. However interferon treatment has been associated with life-threatening hepatitis flares (up to 50%) and infectious complications (28%) in prospective trials of patients with decompensated HBV cirrhosis even when used in very low doses. It is therefore discouraged in patients with decompensated HBV cirrhosis [66]

Lamivudine

Lamivudine is an orally administered nucleoside analogue that inhibits HBVDNA synthesis by incorporating active triphosphate (3TC-TP) into growing DNA chains. Lamivudine can suppress serum HBV DNA to undetectable levels in more than 90% of patients with compensated chronic hepatitis B after 12 month using 100mg of lamivudine daily. It is also associated with improved serum ALT levels and improved liver histology. Compared with interferon lamivudine is safe and well tolerated even in decompensated liver cirrhosis. Hepatitis flares during treatment usually indicate the occurrence of resistant mutations [67, 68]

Once treatment is initiated, it should be maintained indefinitely even in patients who appear to have dramatic clinical improvement and in those undergoing liver transplantation. Unfortunately lamivudine resistance begins after 6 months of treatment, and up to 70% of patients become lamivudine resistant after 5 years of continuous therapy[69] Resistance to lamivudine is manifested by the reappearance of HBV DNA after its initial suppression with a variable increase in serum ALT levels[70]

Adefovir Dipivoxil

Adefovir dipivoxil is a prodrug of adefovir, an acyclic nucleotide analog of adenosine monophosphat Adefovir diphosphate inhibits HBV DNA polymerase by competing with the natural substrate deoxyadenosine triphosphate and by causing DNA chain termination after its incorporation into viral DNA[71] It has a high genetic barrier to resistance and has the ability to suppress most lamivudine-resistant mutants. Renal toxicity is rare with the dose of 10 mg daily. Adefovir dipivoxil has been available for the treatment of chronic hepatitis B since 2003 but has not been evaluated as a primary treatment for patients with decompensated cirrhosis.[71]

Tenofovir

Tenofovir is an acyclic nucleotide analog with a molecular structure similar to that of adefovir. It is approved for the treatment of HIV infection and has in vitro activity against both wild type and lamivudine-resistant HBV. It is a significantly more potent suppressor of HBV replication than adefovir and no drug-resistant variants have been reported with 4 years of continuous treatment in compensated HBV patient [72]

Entecavir

Entecavir is a cyclopentyl guanosine analogue with potent selective inhibition of the priming, DNA-dependent synthesis, and reverse transcription functions of HBV polymerase. It has demonstrated activity against both wild type HBV and, to a lesser extent, lamivudine-resistant HBV, It suppresses HBV replication more rapidly and effectively than lamivudine or adefovir in patients with compensated chronic HBV[73] It has an excellent resistance profile after 5 years in nuycleosid(t)e naïve patients and does not have any reported nephrotoxicity[73]

1:7 Treatments of complications of liver cirrhosis

Gastroscopy should be performed on initial presentation and every two years afterwards in patients with liver cirrhosis to look for oesophageal and gastric varices [75] if found

appropriate treatment should be instituted. Variceal bleeding can be prevented in grade 3 and 4 varices by oral beta blockers and endoscopicvariceal ligation [75]

Treatment of variceal bleeding should include antibiotics to prevent spontaneous septicaemia. Transjugular intrahepatic portosystemic stent (TIPS) placement may be required in patients with uncontrolled or recurrent variceal bleeding. [76]

Liver Transplantation

Patients with advanced irreversible liver failure for which there are no alternative treatments, liver transplant remains the only alternative therapy. All cirrhotic patients with a CP score of more than 7 and a complication of portal hypertension such as ascites, encephalopathy, or variceal bleeding should be referred for liver transplant evaluation [77]**.** Also patients with MELD Score of 17 or more are candidates for liver transplant [21]

Unfortunately liver transplantation is not available to many patients with decompensated liver disease throught the world therefore prevention, and the treatment of the causative agents are the key success in the management of liver cirrhosis.

1.2 PROBLEM STATEMENTS

Chronic liver disease is responsible for over 1.4 million deaths annually and in the western world this disease is among the top ten of disease-related causes of death. The World Health Organization (WHO) estimates that in 2002 liver cirrhosis and primary liver cancer caused 783,000 and 619,000 deaths, respectively. Taken together, these conditions represented approximately one of every forty deaths (2.5%) worldwide. [78]
Chronic hepatitis B virus infection is the leading cause of liver cirrhosis worldwide. In Africa out of 470 million people about 50 million are lifetime carriers of the virus and as many as 12.5 million will die due to hepatitis B induced liver disease.
Clinical presentation of liver cirrhosis is variable. Most frequently it is indolent, asymptomatic and unsuspected until complications are evident. Majority of patients with liver cirrhosis therefore present to the hospital with advanced and irreversible disease.

In Tanzania very little has been published on liver cirrhosis and no studies done regarding clinical presentation and the magnitude of HBV infection among patients with liver cirrhosis.

Scarcity of information on the extent of this problem in our set up may halt the effort to prevent, timely diagnose and give better care to our patients with liver cirrhosis.

1.3 RATIONALE

Liver cirrhosis is an end stage of liver disease with poor prognosis and limited management options whose definitive treatment is liver transplant. However, Liver transplant services are not accessible to majority of patients from developing countries Tanzania included due to lack of expertise and high costs involved in seeking the services elsewhere. Even in developed world where technology and expertise is not problem donor availability is a major challenge.

Despite being preventable and treatable agent, hepatitis B virus has remained to be the leading cause of liver cirrhosis worldwide. Hepatitis B virus infection can be prevented by the readily available vaccine and it can also be treated by the readily available remedies. Even in the presence of liver cirrhosis eliminating the offending cause like treating hepatitis B or C and abstaining from alcohol can prevent progression of disease and hence prolong life. Unfortunately majority of patients with liver cirrhosis present to the hospital at a late stage of their disease when the liver is already decompensated.

Information from this study will give light on the magnitude of the HBV related liver cirrhosis and give a picture about clinical presentation of the patients with liver cirrhosis in Tanzania. This may give the basis for improving the care and practice among patients with liver cirrhosis by promoting hepatitis B vaccination and for routine screening of active carriers.

1.4 BROAD OBJECTIVE

The main objective of this study was to describe the clinical presentations and determine the prevalence of Hepatitis B Infection among patients with liver cirrhosis attended Muhimbili National Hospital (MNH).

1.4. 1 Specific Objective

1. To describe social demographic characteristics of patients with liver cirrhosis attended at MNH.

2. To determine the prevalence of hepatitis B surface antigen among patients with liver cirrhosis attended at MNH.

3. To describe various clinical presentations and its association with HBsAg among patients with liver cirrhosis attended at MNH

4. To describe severity of liver cirrhosis using MELD SCORE and its association with HBsAg among patients with liver cirrhosis attended at MNH.

CHAPTER TWO

2.0 METHODOLOGY

2.1 Study design

The study design was hospital based descriptive study conducted for the duration of 8 month from July 2012 to February 2013

2.2 Study Area

This study was conducted at MNH in medical and surgical gastroenterology units. Both inpatients and outpatients were included. Muhimbili National Hospital is the largest tertiary referral hospital in Tanzania with a bed capacity of about 900 beds. It is also the teaching hospital for MUHAS. It is located in Dar es Salaam, which is the largest commercial city in Tanzania with a population of 4.5 million.

2.3 Study population and participants

The study population was all patients with diagnosis of liver cirrhosis admitted in the gastroenterology unit and those who attended gastroenterology outpatient clinics MNH. All new admission and readmitted patients meeting the criteria were eligible for the study, unless rejected by exclusion criteria.

2.4 Inclusion criteria

All patients with diagnosis of liver cirrhosis aged 18years and above who consented were included in the study.

2.5 Exclusion criteria

Patients who were very sick to be taken for uss and those who died before completing investigations were excluded.

2.6 Sample size calculation

Sample size was calculated using the following formula for finite sample size [79]

$n= [Np (1-p)]/ [d^2/Z^2*(N-1) +p*(1-p)]$

n=Minimum sample size,

N=population size which is the total number of patients with liver cirrhosis attended at MNH during a 1 year period 2011.

Z=Standard normal deviate corresponding to two sided specified significant level. This is 1.96 (at 95%c confidence interval)

d=Margin of error 8%.

P= Prevalence of HBsAg among patients with liver cirrhosis in Kenya 27%. **[78]**

Sample size was (N) = 78.

We included a total of 81 patients with liver cirrhosis diagnosed during the study period.

2.7 Patient Enrollment

Consecutive sampling was used whereby investigator visited gastroenterology unit and general surgical wards every day to look for patients admitted with diagnosis of liver cirrhosis.

Investigator also visited gastroenterology clinic every Wednesday and Thursday to enroll patients who meet the criteria.

All patients with suspected diagnosis of liver cirrhosis admitted and those attending clinic were assessed by proper clinical history, physical examination and by Ultrasound (USS) examination.

Physical examination included general examination and system examination. The diagnosis of cirrhosis was clinically suspected when at least two of the following features were present:

- -Deranged liver function test results suggestive of chronic liver disease with or without jaundice
- Diffuse liver nodularity on palpation
- Clinical signs of portal hypertension including presence of ascites, spleen enlargement, Spider nevi, and palmar erythema

All patients diagnosed clinically to have liver cirrhosis underwent ultrasound examination for confirmation.

2.8 Diagnosis of liver cirrhosis

Diagnosis of liver cirrhosis using ultrasound (type PHILIPS HP 5000with transducer of 5Hz) was made based on the following findings,

- Surface nodularity/irregularity
- Parenchyma heterogenicity
- Intrahepatic vascular narrowing/irregularity

- Portal splenic vascular prominence and spleenomegaly.

A cirrhotic score table designed by Lin et al in 1993 was used to score the parametas of liver cirrhosis. A score of ≥5 was regarded as liver cirrhosis. [80] Using these parametas Lin et al found a sensitivity of 84.6 %, specificity of 79.2 %, positive predictive value of 81.5 %, and negative predictive value of 82.6 %, in detecting cirrhosis. Use of USS in the diagnosis of liver cirrhosis has also been used by Blankson et al in Accra Ghana [81]. In their study the ultrasonographic findings of diffuse liver nodularity with any features of portal hypertension was considered diagnostic of cirrhosis. However they validated their use of USS by gross examination of liver done on autopsy following the dearth of their patients.

Cirrhotic score parameters described by Lin et al.

Score	1	2	3
Liver Surface	Normal	Irregular (like the tooth of the saw)	Roughly irregular or undulating
Parenchyma structure	Normal	Heterogeneous	Roughly heterogeneous
Intrahepatic vessels	Normal	Vessels have normal diameter but unclear view	Vessels are narrowed and irregular
Spleen size index	Normal (Oblique and diagonal diameter multiplication<20cm2)	Large (oblique and diagonal diameter multiplication>20cm2)	

2.9 Data collection methods

Interviewer administered questionnaire was used to collect patient's information regarding;

- Demographic characteristics,
- History of patients illness
- History of alcohol consumption
- 2mls of blood samples were collected from all patients for analysis of;
- ✓ Hepatitis B surface antigen (HBsAg)
- ✓ Liver enzymes
- ✓ Serum albumin
- ✓ Bilirubin levels
- ✓ Serum creatinine
- ✓ HBsAg was assessed using ELISA method.(ABORT (AxSYM)
- ✓ FBP

Structured questionnaire was used to take patient's history. Which included:-

- Demographic characteristics (age, sex, occupation, education and area of residency)
- History of illness (nature, onset, duration, associated symptoms)
- History of hepatitis B vaccination
- History of blood transfusion and intravenous drug injection
- History of alcohol consumption (amount, type and duration)

2.10 Study variables

1. Social demographic variables. Age, sex, occupation, education level and place of residence

2. Clinical history including.

- History of alcohol intake, type, duration and quantity of alcohol beverage consumed.

3. Lab. Studies

   - ✓ HBsAg
   - ✓ Serum albumin
   - ✓ ALAT
   - ✓ ASAT
   - ✓ Bilirubin levels
   - ✓ Creatinine
   - ✓ Urea
   - ✓ FBP

4. Ultrasound findings according to Lin et al cirrhotic score parameters (as seen on the cirrhotic score table above)

2.11 Data entry and analysis

Collected data were checked for quality and coding was done prior to entering into the computer.

Analysis was done using statistical package for social sciences (SPSS) version 16.

The descriptive statistics was computed and comparisons of variables were evaluated.

2.12 Ethical Consideration.

Ethical clearance to conduct the study was sought from Muhimbili University and Allied Sciences Ethical Review Board

Permission to do the study was obtained from the Hospital management

Informed consent to participate in the study was sought from potential study participants.

2.13 Management of patients

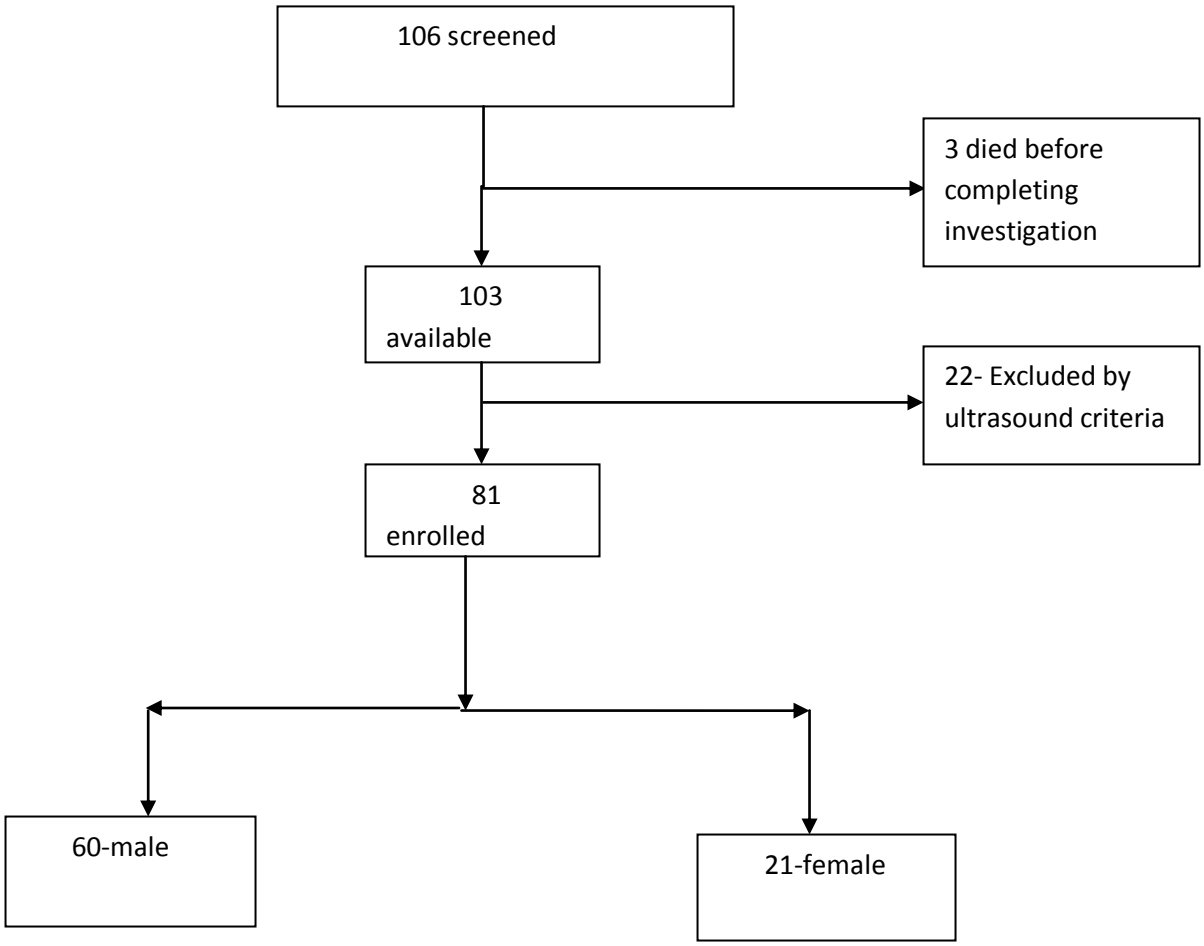
All patients with liver cirrhosis were offered appropriate treatment by investigator in collaboration with unit doctors and counseling required to reduce other risk factors that may worsen prognosis such as alcohol intake was also given.

CHAPTER THREE

3.0 RESULTS

Between the months of July 2012 and February 2013, a total of 106 patients were clinically diagnosed with liver cirrhosis, where by 25 patients did not fulfill the inclusion criteria. These included 3 patients who died before completing investigations and 22 patients who were excluded, as they could not meet the ultrasound criteria as shown in the flow chart below in Figure 1. In total the study included 81 eligible patients where by three quarters were males (n=60).

Figure 1: Flow chart showing patients with liver cirrhosis who were included in the study at MNH (N=106)



3.1 Social demographic characteristics of patients with liver cirrhosis at MNH

The age ranged from 18 to 82 years with the mean of 39.63 years (SD=14.58). Large proportions of them 69% (n=56) were in the age group between 18-40 years. Most of the patients in this study 46(56.8%) were married. More than three quarters of the patients 63 (78%) had primary and below level of education while only 22% had secondary or above level of education. The large proportions of the patients (70.3%) were either peasant or petty traders.

Furthermore in this study large proportion of the patients 51, (63%) reported to have history of alcohol intake where as 8.64% reported to take alcohol until few days before hospital admission. The mean duration of alcohol consumption was 16.67years for males and 14.56 for females. The socio-demographic characteristics of the population of liver cirrhotic patients are as summarized on the Table 1 below.

Table 1: Socio-demographic characteristics of patients with liver cirrhosis attended at MNH between July 2012 and February 2013 (N=81)

Characteristics	Male N=60(%)	Female N=21(%)	Total N=81(%)	P=Value
Age group (years)				
18-40	42 (75)	14 (25)	56 (69.2)	0.727
41-60	10 (66.67)	5 (33.33)	15 (18.5)	
>60	8 (80)	2 (20)	10 (12.3)	
Marital status				
Single	17 (48.57)	18 (51.43)	35 (43.20)	0.158
Married	43 (93.48)	3 (6.52)	46 (56.80)	
Level of education				
Primary and below	45 (71.43)	18 (28.57)	63 (77.80)	0.309
Secondary and above	15 (83.33)	3 (16.67)	18 (22.20)	
Occupation				
Employed	13 (72.22)	5 (27.78)	18 (22.20)	0.321
Unemployed	8 (100)	0	8 (9.90)	
House wife	0	3 (100)	3 (3.70)	
Peasant/pet trader	39 (68.42)	14 (31.58)	57 (70.30)	
Alcohol intake				
Ever	42 (82.35)	9 (17.65)	51 (62.96)	0.027
Current	7 (100)	0	7 (8.60)	0.095
Mean duration of alcohol intake	16.67years	14.56yrs		

3.2 Prevalence of HBsAg among patients with liver cirrhosis at MNH.

Among all patients with Liver cirrhosis almost half of them (48%), were positive for HBsAg

The age group of 18-40 had a largest proportion of patients who were positive for HBSAg as compared to other age groups. Females (57%) had higher proportion of patients with HBsAg positive compared to male (45%). The details of social demographic distribution with HBsAg are as shown in the Table 2 below.

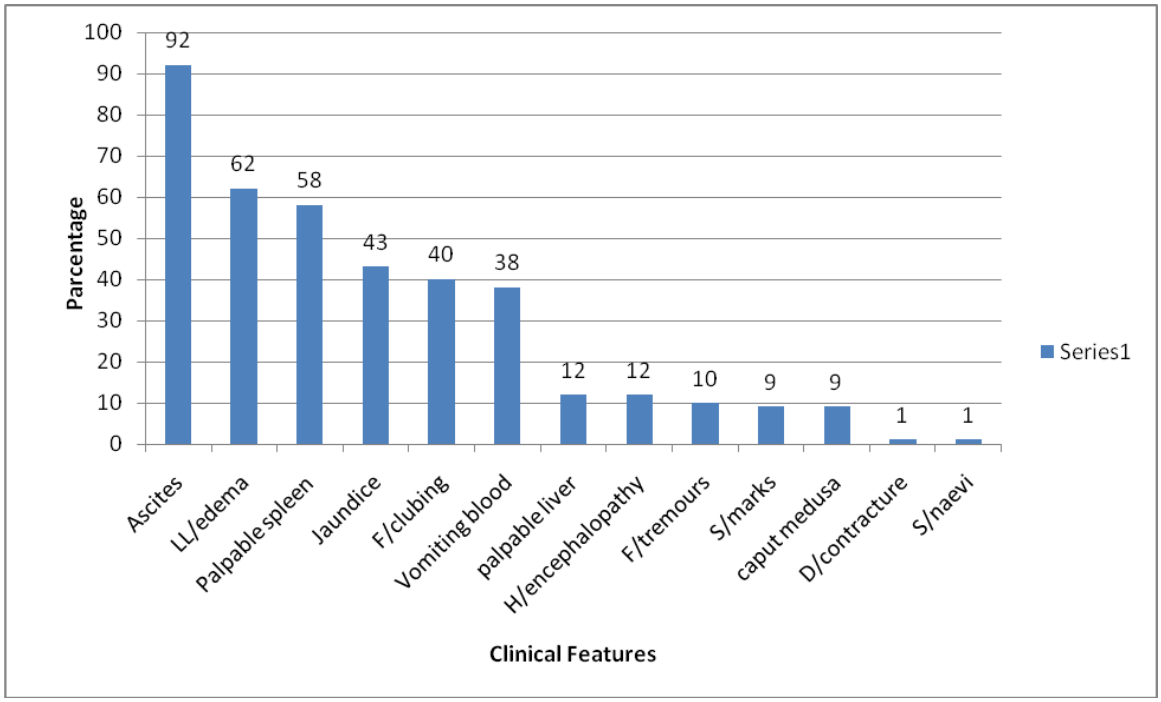
Table 2: Socio-demographic distribution of HBsAg among liver cirrhotic patients attended at MNH in July 2012 and February 2013 (N=81)

Characteristics	HBsAg +ve (%)	HBsAg -ve(%)	Total	P-value
Age group				
18-40	29 (52)	27(48)	56(100)	0.695
41-60	6 (40)	9(60)	15(100)	
>60	4 (40)	6(60)	10(100)	
Gender				
Male	27(45)	33(55)	60(100)	0.44
Female	12(57)	9(43)	21(100)	
Level of education				
Primary and below	28(47)	31(53)	59(100)	0.44
Secondary and above	11(61)	7(39)	18(100)	
Marital status				
Single	10(43)	13(57)	23(100)	0.448
Married	29(50)	29(50)	58(100)	
0ccupation				
Employed	8(44)	10(56)	18(100)	0.627
Unemployed	5(63)	3(37)	8(100)	
Peasant/petty trader	24(46)	28(54)	52(100)	
House wife	2(67)	1(33)	3(100)	
Alcohol intake				
Ever	24(47)	27(53)	51(100)	0.822
Never	15(50)	15(50)	30(100)	

3.3 Clinical presentations of patients with liver cirrhosis at MNH

With regard to clinical presentation a large proportion of the patients (91.4%) had ascites, followed by lower limb edema and enlarged spleen. Other stigmata's of chronic liver disease like spider naevi or Dupyutrens contracture were seen in very minority of patients. The details are as shown in Figure 2 below.

Figure 2: Percentage distribution of Clinical features among patients with liver cirrhosis



There was equal distribution of clinical features with regard to gender and age group except for flapping tremors which was seen more among older age group as shown on table 3 and 4 below. Furthermore no association was found between various clinical features and HBsAg positivity.

Table 3: Pattern of Clinical features by gender among patients with Liver Cirrhosis attended at MNH

Clinical features	Gender		
	Male (%)	Female (%)	P-value
Ascites			
Yes	54 (90)	20 (95.2)	0.67
No	6 (10)	1 (4.8)	
Jaundice			
Yes	29 (48.3)	6 (28.6)	0.116
No	31 (51.7)	15 (71.4)	
Lower limb edema			
Yes	39 (65)	11 (52.4)	0.434
No	21 (35)	10 (47.6)	
Palpable spleen			
Yes	36 (60)	11 (52.4)	0.612
No	24 (40)	10 (47.6)	
Palpable liver			
Yes	8 (13.3)	2 (9.5	0.895
No	51 (85)	18 (85.7)	
Caput medusa			
Yes	5 (8.3)	2 (10)	0.999
No	55 (91.7)	18 (90)	
Scratch marks			
Yes	4 (6.7)	3 (14.3)	0.368
No	56 (93.3)	18 (85.7)	
Spider naevi			
Yes	6 (10)	3 (14.3)	0.689
No	54 (90)	18 (85.7)	
Finger clubbing			
Yes	27 (45)	5 (23.8)	0.121
No	33 (55)	16 (76.2)	
Duputrens contracture			
Yes	1 (1.7)	0	0.999
No	59 (98.3)	21 (100)	
Flapping tremors			
Yes	5 (8.3)	3 (14.3)	0.673
No	55 (91.7)	18 (85.7)	
Hepatic encephalopathy			
Yes	6 (60)	4 (40)	0.278
No	54 (76.1)	17 (23.9)	

Table 4: Pattern of Clinical features by age group among patients with Liver Cirrhosis attended at MNH: N=81

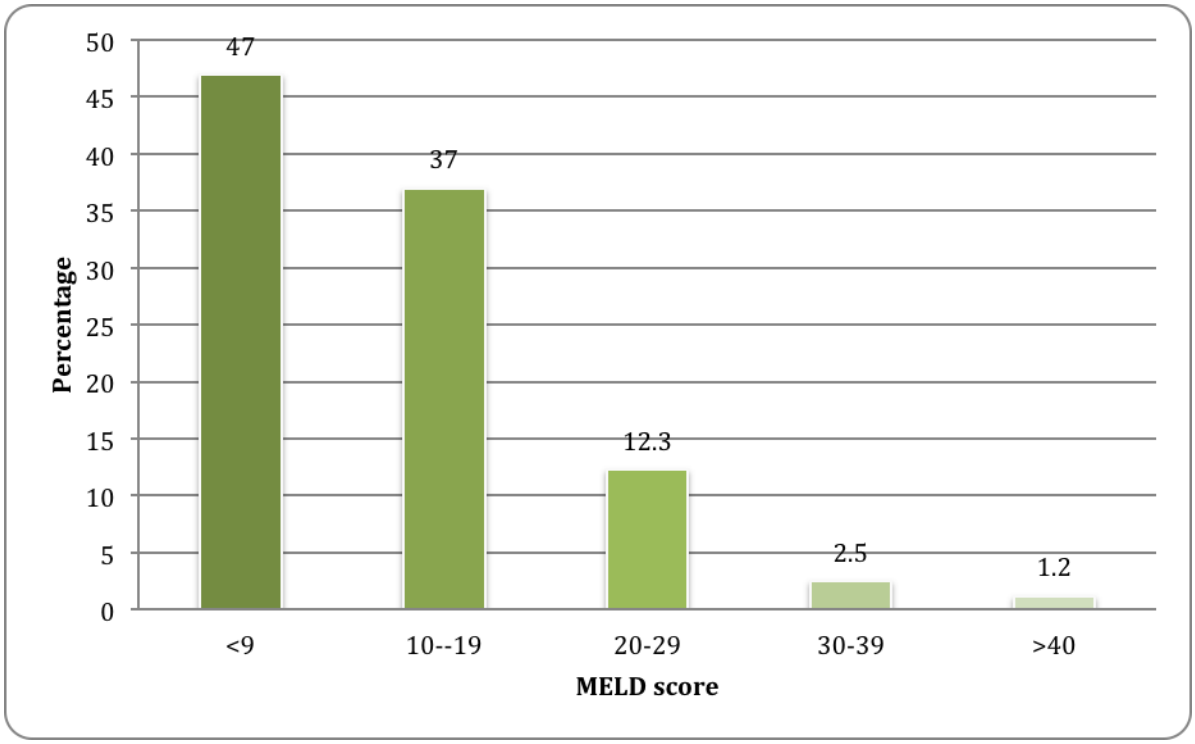
	Age group			p-value *
Clinical features	18-40 (%)	41-60 (%)	>60 (%)	
Jaundice	26 (74.30)	6 (17.10)	3 (8.60)	0.614
Ascites	52 (70.20)	13 (17.60)	9 (12.20)	0.740
Lower limb edema	33 (66)	8 (16)	9 (18)	0.140
Palpable spleen	36 (76.60)	7 (14.90)	4 (8.50)	0.220
Palpable liver	5 (50)	4 (40)	1 (10)	0.183
Caput medusa	4 (57.10)	1 (14.30)	2 (28.60)	0.380
Scratch marks	3 (42.90)	3 (42.90)	1 (14.20)	0.102
Spider naevi	6 (66.70)	2 (22.20)	1 (11.10)	0.867
Finger clubbing	20 (62.40)	6 (18.80)	6 (18.80)	0.351
Flapping tremors	3 (42.90)		4 (57.10)	0.012

*For cells with value less than 5, Fisher's exact test was used instead of Pearson's chi-square

3.4 MELD score distribution among patients with liver cirrhosis at MNH

As for severity of liver cirrhosis MELD score was calculated and categorized as described in the methodology. Most of the patients (46%) had three months-mortality risk of 2%, while 37% had mortality risk of 6% as shown in the Figure 3 below. About 22% of the patients were eligible for liver transplant i.e. had MELD score of 17 or greater.

Figure 3: Showing percentage distribution of patients with liver cirrhosis according to MELD score



Associations of different clinical features with MELD score were done using t-test. It was found that MELD score was significantly higher among those with ascites and jaundice as shown in Table 5 below. Furthermore there was no statistical difference in mean MELD score between those who were HBsAg positive and those who were HBsAg negative. (p=0.155)

Table 5: Relationship between mean MELD score and clinical feature among liver cirrhotic Patients admitted at MNH: N=81

Clinical features	Mean MELD score	p-value
Ascites		
Yes	12.58	0.014
No	4.59	
Jaundice		
Yes	14.37	0.018
No	10.01	
Lower limb edema		
Yes	0.22	0.952
No	0.22	
Palpable spleen		
Yes	11.19	0.372
No	12.86	
Palpable liver		
Yes	14.81	0.242
No	11.46	
Caput medusa		
Yes	14.94	0.332
No	11.75	
Scratch marks		
Yes	12.34	0.999
No	11.54	
Spider naevi		
Yes	12.64	0.775
No	11.8	
10.finger clubbing		
Yes	13.17	0.264
No	11	
Duputrens contracture		
Yes	12.4	0.953
No	11.9	
Flapping tremors		
Yes	11.8	0.975
No	11.9	

CHAPTER FOUR

DISCUSSION

This study found that the mean age of the respondents was around 39 years most of them being male, married, peasants or petty trader and had primary level of education. Almost half of the studied sample tested positive for HBsAg though was not associated with any tested variable. Ascites was the commonest clinical presentation followed by Lower limb edema and splenomegaly (all these present in more than half of the sample). About a quarter of the patients were eligible for liver transplant.

4:1Social demographic characteristics

The young age of the patients seen in this study as well as male preponderance was also seen in other studies done in most countries of Africa.[5, 78] The young age of the patients in this study can reflect the preponderance of infection acquired early in life. (Perinatal HBV transmission)

The large proportion of the patients in this study (63%) used to drink alcohol with a mean duration of alcohol consumption of 16.71 years and about 8.64% were still taking alcohol few days before hospital admission. Alcohol abuse has been claimed as one of the most important causes of liver cirrhosis. [82] In Europe, alcohol has been reported to cause 25–65% of cirrhosis [83].

Intake of alcohol of more than 30g/day for 10 to 15 years has shown to have strong association with liver cirrhosis[7]. In this study Local alcohol consumption was predominant over standard alcohol making quantification difficult.

4:2 Prevalence of HBsAg among patients with liver cirrhosis at MNH.

In this study almost half 48% of all patients with liver cirrhosis were HBsAg positive. This findings are nearly similar to studies done in most parts of Africa [78] except some few countries of western Africa where the prevalence as high as 84% among patients with liver cirrhosis has been reported**.** As pointed out in the literature hepatitis B is

endemic in Africa with a seroprivalence in adults ranging from 56 to 92 percent. [50]. The prevalence of hepatitis B surface antigen positivity in the general population across African countries is approximately 5 to 20 percent [49] In Tanzania prevalence of hepatitis B was reported to be 70.7% and HBsAg prevalence of 6 to 8 percent in the general population. In their study Joseph et al found that the overall prevalence of HBsAg for African countries among patients with liver cirrhosis is 44%, while Europe and America has the lowest prevalence of 6 and 13 respectively. It has been reported that up to 95% of children under five years of age infected with HBV become chronic HBV carriers and that one third of chronic carriers will develop progressive liver disease including cirrhosis and primary liver cancer[84] leading to death in 15-25%. The regional differences in prevalence of HBsAg among patients with liver cirrhosis may reflect the aetiological differences of liver cirrhosis among different regions.

In this study although there was no significant statistical difference noted in HBsAg positivity between male and female but overall majority of patients with liver cirrhosis in this study were males (74%) This findings correlate well with worldwide studies of liver cirrhosis which also showed male preponderance. [78] A finding which may suggest a male pre-disposition to various risk factors for liver cirrhosis hepatitis B virus and alcohol included.

4:3 Clinical presentations of patients with liver cirrhosis at MNH.

Similar to literature from other parts of Africa [5], the majority of the patients in this study came late with decompensated liver cirrhosis. In this study commonest clinical presentations were ascites, LL edema and jaundice. This also correlates well with other studies done in Africa [5]. In his study regarding the etiology and complications of liver cirrhosis Abdelsalam also found ascites to be the commonest symptom [5] the finding of ascites as the commonest symptom in majority of patients mean that patient with liver cirrhosis present to the hospital with very advance liver cirrhosis. The prognosis of liver cirrhosis ranges according to the severity of the liver disease and is significantly reduced after decompensation of liver function developes. Based on International Consensus Workshop of Baveno[2] large proportion of our patients had decompensated liver

cirrhosis (stage 3 or 4). This indicates poor prognosis among these patients, as the calculating annual mortality rates for stage 3 and 4 are 20 and 57% respectively. The rate of variceal bleeding is approximately 10-30% per year [2]. About 31% of our patients in this study reported to have history of vomiting blood which may be a harbinger of underlying variceal bleeding. Unfortunately we could not do gastroscopy to all of our patients in this study due to various reasons such as frequently breakdown of our endoscopy machine and limitation of budget to do it elsewhere. Clinical signs were almost equally distributed between the age groups except for Flapping tremors which were seen more significantly among elderly group. However this may be due to the tremors related to advanced age or degenerative diseases rather than the true flapping tremors of end stage liver disease.

4:4 severity of liver disease as assed by MELD score.

In this study large proportion of patients had MELD score of 19 and below. As pointed out in the literature MELD scores can be applied to predict 3-month mortality among patients with end stage liver disease. The score is also useful for allocating patients for liver transplant. Based on the MELD score findings in this study about 22% were in the range of those in need of liver transplant as they had a MELD score of more than seventeen. Presence of ascites and jaundice was associated with significant higher mean MELD score than when these features were absent. However jaundice is not a common presentation among cirrhotic patients and therefore this finding can be due to other hepatic diseases such as malignancy rather than true cirrhosis. Nevertheless these features can be of predictive value for early mortality among patients with liver cirrhosis in our setting.

CHAPTER FIVE

5.1 CONCLUSSIONS

This study shows that Liver cirrhosis is a common problem among patients admitted at MNH whereby it is more common in males. Prevalence of HBsAg among patients with liver cirrhosis in this study is high (48%) Majority of patients with liver cirrhosis attending MNH come late with decompensated liver cirrhosis. Large proportion (84%) of patients with liver cirrhosis in this study had low MELD score.

5.2 RECOMMENDATIONS

Universal immunization coverage with hepatitis B vaccine in infants, the intervention that was started in 2002, should be encouraged to reduce the incidence of HBV-related chronic liver diseases. In view of the high prevalence of HBsAg among patients with liver cirrhosis in this study and because hepatitis B virus is blood born virus we also recommend hepatitis B vaccination to health care providers of Tanzania emphasis being put to those at risk of contact with body fluids. Given the chronic alcohol intake in the majority of study participant the risk that could also contribute to the disease under study we recommend health promotion to the community to raise awareness about adverse effects of excessive chronic intake of alcohol to the liver.

Whether alcohol is the cause of liver cirrhosis in this study especially in those patients with negative HBsAg a it cannot be proved in this study.

5.3 LIMITATIONS OF THE STUDY

Although the prevalence of HBsAg among patients with liver cirrhosis in this study is high, causality could not be determined because no control group was used. Furthermore despite the fact that large proportion of the patient 63% reported history of chronic alcohol drinking, varieties of local brew consumption was predominant as compared to standard liquors making alcohol level quantification and comparison difficult. Whether alcohol or HBV could be the cause of cirrhosis cannot be concluded from this study.

Despite the use of clinical and radiological criteria in the diagnosis of liver cirrhosis, it is clearly documented that the gold standard for diagnosis of liver cirrhosis is by histopathological examination through biopsy. USS for example may miss some cirrhosis especially micro nodular type and cannot precisely rule out liver malignancies. Unfortunately liver biopsy was not possible in this study, as it is not routinely done at MNH due to lack of facilities. Blankson et al validated their use of Ultrasound in diagnosis of liver cirrhosis by performing autopsy following the dearth of their patients, it was not possible in our study to do autopsy as the three patients who died USS was not yet done.

The small sample size in this study may compromise the significance level of most of the bivariate analyses done.

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APPENDICES

Appendix i: Questionnaire

Q/N ----------

Hospital registration number----------

Part 1: demographic data.

1. Date of interview---/---/----

2. Name----------

3. Sex

1. Male

2. Female

4. Date of birth-----/-----/------- (dd/mm/yyyy)

5. Place of birth 1.district ----------

2. Ward----------

6. Religion 1.Christian
2. Muslim
3. Others specify----------

7. Marital status. 1. Never married
2. Married
3. Divorced
4. Cohabiting

5. Widdowed

8. Level of education, 1.none
   2. Primary school
   3. Secondary school
   4. Post secondary

9. What is your occupation?
   1. Peasant
   2. Pety trader
   3. Employed
   4. Not employed
   5. Housewife
   6. Others (mention)

10. Do you drink alcohol?
   1. Never
   2. Yes but I stoped
   3. Yes until now

11. How long have you been drinking
   1-------months
   2--------years

12. When did you stopped drinking
   1-------months
   2-------years

13. Which type of alcohol do/did you drink?
   1. Beer
   2. Whisky
   3. Gin
   4. Gongo

5. Mnazi
6. Kibuku
7. Komoni
8. Mbege
9. Any other---------

14. How much do/did you drink per day?

---------- (estimates in mills)

15. How much do/did you drink per week

---------- (estimates in mills)

16. Have you been vaccinated for HBV?

1. Yes
2. No

17. If yes at what age ----------years

18. Any history of blood transfusion

1. Yes
2. No

19. If yes how many years ago. ----------years

20. Any history of intravenous drug use

1. Yes
2. No

21. If yes for how long --------years

22. Are you sexual active?

1. Yes
2. No

23. At what age did you begin sexual intercourse ---------years

24. Number of sexual partners in a life time----------

25. Do/did you use condoms regularly during intercourse?

    1. Yes
    2. No

Part 2. Physical signs.

26. Temperature-------^{o}C

27. Weight---------kg

28. Height---------cm

29. BP----------mmhg

30. LN palpable 1. yes 2.no

31. LL edema 1.yes 2.no

32. Jaundice 1.yes 2.no

33. Finger clubbing 1.yes 2.no

34. Palma erythema 1.yes 2.no

35. Flapping tremors 1.yes 2.no

36. Dupuytrens contracture 1.yes 2.no

37. Spider naevi 1.Yes 2.No

38. Scratch marks 1.Yes 2.No

39. Caput medusa 1.Yes 2.No

40. Spleen palpable 1 Yes 2.No

41. Liver palpable 1.Yes 2.No

1. Liver span-------cm

2. Tendernes 1.yes 2.no

3. Surface – 1.Smooth---- 2.Rough--- 3.Nodular----

42. Ascites 1.Yes 2.No

43. Respiratory examination

1. RR------/min
2. Consolidation 1.Yes 2.No
3. Pleural effusion 1.Yes 2.N0
4. Crackles 1.Yes 2. No

44. CVS

1. HR-------/min
2. Cardiomegaly 1.Yes 2.No
3. Pericardial effusion 1.Yes 2.No
4. Valvular heart disease 1.Yes 2.No

45. CNS examination

Alertness 1.Yes 2.No

Orientation 1.Oriented 2.Dysiorienred

Memory 1.Intact 2.Impared

Confused 1.Yes 2. No

Consciousness GCS-------/15

Hepatic encephalopathy Grade----------

Appendix ii: Consent Forms English

CLINICAL PRESENTATION AND MAGNITUDE OF HEPATITIS B INFECTION AMONG PATIENTS WITH LIVER CIRRHOSIS ATTENDING MNH

Greetings madam / sir.

My name is Dr. Wolfgang Bernard a resident in the department of internal medicine. I am conducting a research on clinical presentation on patients with liver cirrhosis and the magnitude of hepatitis B virus in these patients.

Purpose of the study.

We are recruiting patients with liver cirrhosis to determine their clinical presentation and the presence of hepatitis B virus among those patients, which is the commonest microorganism known to cause liver cirrhosis.

What participation involves:

Patients willing to participate will be interviewed on some questions related to the research which will include their social demographic characteristics and medical history. It will also include physical examination, abdominal ultrasound examination and taking blood for hepatitis B detection.

Risks:

There are no risks associated with taking these measurements

Benefits:

Patients found to have liver cirrhosis will be counseled and treated and those found to have hepatitis B infection will be offered appropriate medications.

Confidentiality:

Any results from the patient will not be revealed to anybody except attending doctors and the patient himself.

Costs.

No payment will be requested from you as a fee to participate in the study.

Voluntary participation and Rights to withdraw.

Your participation is voluntary and you have the right to discontinuer from participating in our study at any time. However your decision will not affect in anyway your right to care and treatment.

Person to contact in questions or any problems regarding this research.

Dr. Wolfgang Bernard 0713132451, principal investigator.

Dr. Ewaldo Komba 0713200171. Lecturer at Muhimbili University.

In case of any information about your rights as a participant in this study please contact.

Professor Muhsin Aboud

Director of research and publications Muhimbili University of Health and Allied sciences (MUHAS)

P. O. Box 65001 Dar es salaam.

Tel 2151489

I …… have read/been told of the contents of this form and understood its meaning. I agree to participate in this study.

Signature …….. (Participant) date ……..

Signature ……. (Researcher) date ……

Appendix iii: Consent Form – Swahili

Fomu ya ridhaa katika utafiti wa mnyauko wa ini,dalili zake na uwepo wa virusi vya hepatitis B kwa wagojwa wanaotibiwa hospitali ya taifa muhimbili.

Utambulisho.

Habari za saa hizi, jina langu ni Dkt Wolfgang Bernard mwanafunzi wa digrii ya pili ya udaktari katika chuo kikuu cha muhimbili. Pia nafanya utafiti kwa wagonjwa wenye tatizo la ini kusinyaa, dalili zake na uwepo wa virusi vya homa ya manjano.

Malengo ya utafiti.

Utafiti huu unafanyika kwa wagonjwa wenye shida ya ini kusinyaa kuangalia dalili zake pamoja na uwepo wa virusi vya homa ya njano kwa wagonjwa hawa.

Ushiriki unahusisha nini.

Wagonjwa watakaokubali kushiriki tutawahoji maswali kadhaa kuhusiana na maisha yao na ugonjwa wao na kisha tutawapima na kuwafanyia altrasaundi ya tumbo na kuwachukua damu kwa ajili ya kupima virusi vya homa ya manjano.

Faida na athari.

Hakuna athari zozote utakazopata kulingana na utafiti huu zaidi ya maumivu kidogo wakati wa kutoa damu.

Garama za kujiunga na utafiti

Hautaingia garama zozote kushiriki katika utafiti huu.

Kushiriki kwa hiari na haki ya kujitoa.

Kushiriki katika utafiti huu ni kwa hiari na unaweza kujitoa wakati wowote. Vyovyote vile uamuzi wako hautaathiri mwenendo wa matibabu yako.

Ukiwa na maswali au shida wakati wowote kuhusiana na utafiti huu wasiliana nami

Daktari Wolfgang Bernard, simu 0713132451 mtafiti mkuu au

Dokta Ewaldo komba, simu 0713200171 msimamizi wangu katika utafiti huu.

Iwapo utakuwa na swali lolote kuhusu haki zako kama mshiriki katika utafiti huu wasiliana na

Profosa Muhsin Aboud mkurugenzi wa kamati ya utafiti na matoleo Chuo Kikuu cha Afya na Sayansi za Tiba Muhimbili.

S.L.P 65001 Dar es Salaam, simu 2151489.

Ntashukuru kwa ushiriki wako katika utafiti huu.

Mimi …….. nimeelezwa/nimesoma yaliyomo katika fomu hii na nimeelewa maana yake. Nakubali kushiriki katika utafiti huu.

Sahihi …… (Mshiriki) Tarehe …….

Sahihi …… (Mtafiti) Tarehe ……

Appendix iv: Laboratory Form

TEST	**RESULTS**
ALAT	
ASAT	
BIL T	
BIL D	
Hb	
MCV	
MCH	
WBC	
NEUTROPHIL	
LYMPHOCYTE	
EOSINOPHIL	
BASOPHIL	
PLATELATES	
HBsAg	
CREATININE	
UREA	