CORRELATION OF HEPATOBILIARY ULTRASOUND FINDINGS WITH LIVER ENZYME ASSAYS IN ADULT PATIENTS WITH JAUNDICE AT MOI TEACHING AND REFERRAL HOSPITAL-KENYA.

BY

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A research thesis presented in partial fulfillment of the award of the degree of Master of Medicine in Radiology and Imaging of Moi University.

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Student's Declaration

I declare that this is my original work and has not been presented in any other university or institution for an award of a degree or any academic credit. No part of this work may be reproduced or transmitted in any form without prior permission from the author or Moi University

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DEDICATION

To my lovely wife Grace, for the unwavering support in everything I do. To my children Samora and Sophie, you inspire me to work hard every single day. To my dad, for impressing upon us the need to excel in our education. To my late mum, you left us all too soon.

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LIST OF ABBREVIATIONS

ALP Alkaline phosphatase

ALT Alanine aminotransferase

AST Aspartate aminotransferase

DBIL Direct Bilirubin

D/T Direct Bilirubin/ Total Bilirubin

GGT Gamma glutamyl transpeptidase

IREC Institutional Research and Ethics Committee

KNH Kenyatta National Hospital

MTRH Moi Teaching and Referral Hospital

TBIL Total Bilirubin

US Ultrasound

ABSTRACT

Background: Jaundice is a common manifestation of hepatobiliary disease and is associated with significant morbidity and mortality. The differential diagnosis of jaundice and subsequent management of these patients heavily relies on ultrasound and serum liver enzyme findings. Correlation of the two is therefore important in making clinical decisions.

Objective: To describe the hepatobiliary ultrasound findings and determine their correlation with serum liver enzymes among adult patients with jaundice at Moi Teaching and referral Hospital, Eldoret, Kenya.

Methods- This was an analytical cross-sectional census study conducted at Moi Teaching and Referral Hospital, Eldoret, Kenya between October 2015 and September 2016. Seventy-nine patients aged 18 years and above with jaundice, who had bilirubin as well as liver enzyme test results, and had hepatobiliary ultrasound scans done were enrolled. All the sonograms were reviewed by two consultant radiologists. Ultrasound findings were documented and correlation done with serum liver enzymes. Data was collected using a structured questionnaire and analysis was done using STATA version 13E software. Descriptive statistics were summarized for patient socio-demographics. Frequency tables were generated for categorical variables. Results were presented using tables and charts.

Results: Median age of the participants was 34 years (IQR 22-50). Overall, the most common cause of jaundice as determined by ultrasound was acute inflammation of the liver (38%) with reduced echogenicity and a starry sky appearance, followed by pancreatic head mass and liver fibrosis/cirrhosis (11% and 10% respectively). Hepatocellular category of jaundice constituted 56% of the participants while obstructive jaundice constituted 31%. Thirteen per cent of the participants had normal ultrasound findings. Correlation with liver enzymes showed a significant difference in the median ratio of alanine transaminase (ALT): alkaline phosphatase (ALP), also known as the R-value, between obstructive jaundice (R-value 0.15; 95% CI 0.05-0.25) and hepatocellular jaundice (R-value 2.17; 95% CI 0.43-7.3); p0.0001.

Conclusion: Acute inflammatory conditions of the liver were the commonest ultrasound finding among adult patients with jaundice, with pancreatic head mass being the commonest among the obstructive type of jaundice. This study has also shown that there is a statistically significant difference between the alanine transaminase: alkaline phosphatase ratio (R-value) for hepatocellular and obstructive jaundice as seen on ultrasound.

Recommendation: There should be a high index of suspicion for acute inflammatory conditions of the liver and pancreatic head masses when scanning younger and elderly patients with jaundice respectively. Also, a larger study is recommended to check for true associations between the ALT: ALP ratio (R-value) and hepatocellular and obstructive types of jaundice.

CHAPTER ONE: INTRODUCTION

1.1 Background Information

Jaundice, also known as icterus, is the yellowish pigmentation of the skin, the conjuctival membranes over the sclera and other mucous membranes caused by hyperbilirubinaemia (Jerry T.M. et. al 1992). Concentration of bilirubin in plasma is normally below 1.2mg/dl (<25micromol/litre). A concentration higher than approximately >50micromols/litre leads to jaundice (Despopoulas et. al. 2009). Bilirubin is derived as a breakdown product of haem molecules (RUDRALINGAM and Sukumar 2013).

Increased bilirubin in blood can result from increased production of bilirubin, impaired transport of bilirubin to the liver for excretion or decreased excretion of bilirubin (Kisper. Fuci 2000).

Increased production: Bilirubin is a product of breakdown of hemoglobin released from the red cells. The causes of this type of jaundice thus include hemolytic anemias and malaria.

Impaired transport: This may be a result of advanced Congestive Heart Failure causing cardiac cirrhosis

Decreased excretion: This category includes conditions in which the capacity of the liver to transform unconjugated bilirubin to conjugated bilirubin (e.g Hepatitis and liver cirrhosis) and conditions in which transfer of conjugated bilirubin into the bile ducts is impaired (e.g Dubin-Johnson syndrome) as well as conditions in which the bile ducts are obstructed (e.g Common bile duct stones and pancreatic head masses).

Jaundice can be categorized into obstructive, hepatocellular, hemolytic or congenital non haemolytic types (Yu, Fu et al. 2012). Differentiating between obstructive and hepatocellular categories is critical in management. In the differential diagnosis of jaundice a combination of liver enzyme assays and US findings is used. The primary aim of imaging is to assess whether the cause of jaundice is obstructive & to determine the cause of obstruction when present. US is the first line imaging modality for assessment of jaundice. It is quick, cheap and effective in diagnosing biliary dilatation.

Two Patterns of liver enzyme derangement have been described. These are obstructive & hepatocellular patterns. In obstructive pattern there is predominant elevation of bilirubin, ALP, & GGT while in hepatocellular pattern, there is predominant elevation of bilirubin, AST, & ALT. These patterns are said to be non-specific and significant overlap has been reported (Kumar and Bhatia 2011, Saboo, Vijaykumar et al. 2012).

Recent findings suggest that the R-value (ALT/ALP) may be applied in the differentiation of general obstructive & hepatocellular jaundice (Yu, Fu et al. 2012). For hepatocellular for hepatocellular jaundice, R values of 1-10 are suggestive while for obstructive jaundice, R values of 0.4- 0.75 are suggestive. R-values ranging from 0.75-1.0 suggest a mixed picture.

Anatomy of the liver and the biliary system

The liver is the largest internal organ in the body, accounting for approximately 2% to 3% of the total body weight of an adult (Skandalakis, Skandalakis et al. 2004). It is found in the right upper quadrant of the abdomen.

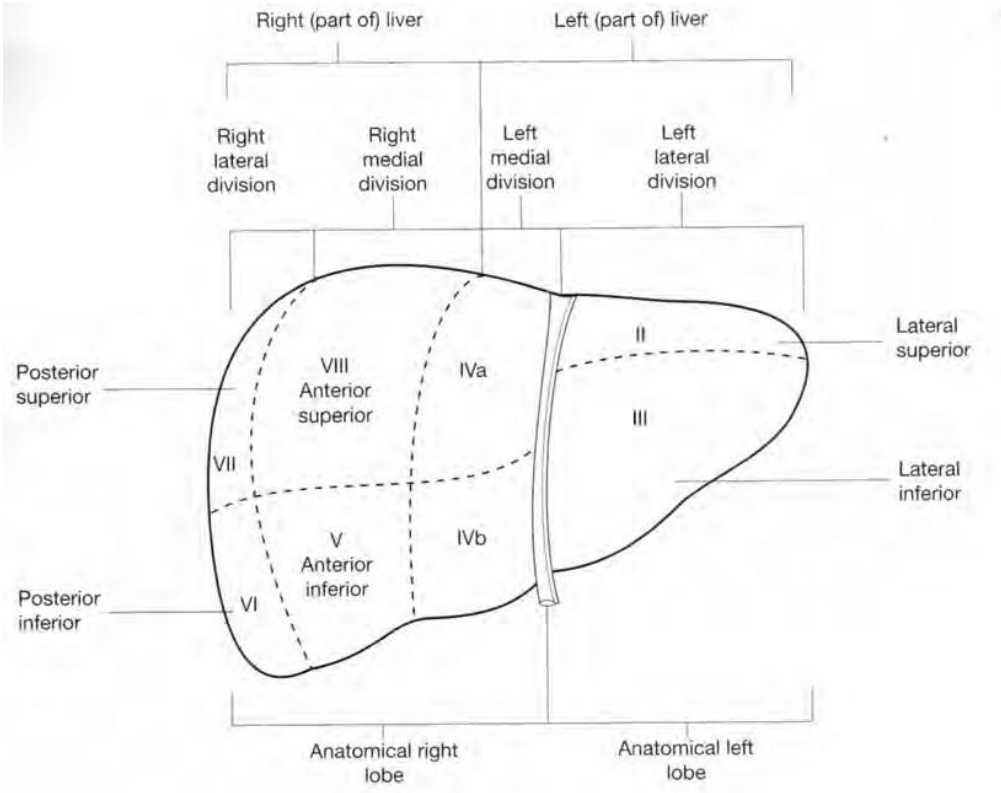
Segmental liver anatomy

The liver is comprised of two functionally independent right and left lobes, defined by the arterial distribution. Each is supplied by the right and left portal veins and the right or left hepatic arteries, and each drained by the right or left hepatic duct. The plane of division between these lobes is called the principal plane. This plane lies parallel to and about 4 cm to the right of the attachment of the falciform ligament. On the visceral surface the principal plane is defined by the IVC superiorly and the gallbladder bed inferiorly. The hepatic veins do not run with the structures of the portal triad (portal vein, hepatic artery and bile duct) but are inter-segmental, draining portions of adjacent segments. The middle hepatic vein lies in the principal plane and drains from both lobes.

In current terminology, the left lobe includes the caudate lobe. This is defined by the distribution of the left hepatic artery. The right hepatic artery supplies a variable portion of the quadrate lobe. In 5-10% of females and rarely in males, the lower border of the right lobe, a little to the right of the gallbladder, may project downwards for a considerable distance as a broad tongue-like or bulbous process called Reidel's lobe. This is not a true lobe.

Further subdivision into segments is based on branches of the right and left hepatic arteries.

Figure 1: A diagram of Couinaud's classification of the liver



Adapted from Anatomy for Diagnostic imaging by Stephanie Ryan, 2nd Edition 2004, Page 172

Segments are numbered in the Couinaud system in a clockwise direction starting at the caudate lobe. The caudate lobe is segment I. Segments II and III are the furthest left, divided by the left hepatic vein from segment IV. The left portal vein separates segment II above from segment III below. Segment IV lies between the left hepatic vein and the middle hepatic vein. It is divided into segment IVa above and IVb below by the left portal vein. The right lobe has four segments, divided by the right hepatic vein into anteromedial and posterolateral divisions and by the plane of the right branch of the portal vein into superior and inferior sections. These four segments are numbered in a

clockwise fashion from anterior inferomedial: V, VI, VII and VIII. The segments may also be named descriptively according to their location, e.g. posterior segment (caudate), right posterior lateral, posterior medial, anterior lateral and anterior medial segments, and left medial superior, medial inferior and lateral segments.

The functional subunit of the liver is the microscopic lobule, which has a central vein and, in spaces between the lobules, portal canals or triads, each with a branch of the hepatic artery, portal vein and bile duct. The old anatomical description of the liver as having a large right lobe and small left lobe separated by the falciform ligament defines the anatomical left lobe as consisting only of segments II and III.

The Biliary System

Consists of:

- The intrahepatic ducts
- The extrahepatic biliary tract which comprises: The right and left hepatic ducts, the common hepatic duct, cystic duct, gall bladder and common bile duct.

Drainage of bile is usually from the interlobular bile ducts to septal bile ducts into the left and right and left hepatic ducts before the two hepatic ducts join to become the common hepatic duct.

The extrahepatic ducts:

The right and left hepatic ducts join at the hilum to form the common hepatic duct (CHD). The CHD then joins the cystic duct to form the common bile duct (CBD). The CBD then passes inferiorly and posteriorly to the first duodenal part and head of the pancreas to terminate in the second part of the duodenum at the hepatopancreatic ampulla of vater. The CBD measures 8-10cm long and 5-6mm in diameter.

The cystic duct measures 3-4cm in length and has mucosal folds the spiral valves of heister that control the release of bile from the gall bladder.

The gall bladder

Is a pear shaped fibromuscular structure located within the gall bladder fossa of the liver. It measures 7-10cm in length with a wall thickness of 2-3mm. The gall bladder serves to store and concentrate bile. It has a fundus, body and a neck that continues into the cystic duct.

The Pancreas

The pancreas consists of the head, neck, body and the tail, with the pancreatic head being the most important part in jaundice manifestation. A pancreatic head mass can compress the CBD leading to obstruction of bile flow.

Proper and timely diagnosis is key in the management of patients presenting with jaundice, for some of the underlying conditions like biliary obstruction are amenable to surgery.

Sonography is the recommended initial imaging test in evaluation of patients presenting with jaundice (Foley W.D. et. al. 2007). It is the least invasive modality for imaging the hepatobiliary system. Unlike Computed Tomography Scanning and Magnetic Resonance Imaging, the technique is portable, quick and cheaper. Ultrasound uses no ionizing radiation and is therefore the technique of choice in pregnant women, in patients with contrast allergies or in patients in whom MRI is contraindicated (Bennett and Bova 1990).

The causes of jaundice can usually be grouped into four broad categories: Cholestatic (obstructive) jaundice, hepatocellular jaundice, hemolytic jaundice and congenital non-hemolytic jaundice. Hepatocellular and cholestatic jaundice are the most common (Yu, Fu et al. 2012).

The commonest causes of jaundice include bile duct stones, pancreatic cancer, cholangiocarcinoma, alcoholic liver disease, drug induced hepatitis and viral hepatitis (Taylor, Stapley et al. 2012)

In cases of jaundice and other liver related conditions, there is often a biochemical derangement. Liver function tests (LFTs) including serum liver enzymes and bilirubin levels are a helpful screening tool in detecting hepatic dysfunction (Thapa and Walia 2007). The pattern of liver enzyme alterations is often the first piece of evidence the physician has. This is because common causes of liver disease have typical patterns (Giannini, Testa et al. 2005).

1.2 Problem Statement

Jaundice is a common finding in patients with various hepatobiliary pathologies and has been found to have high morbidity and mortality if not diagnosed early (Hawkins, DeMatteo et al. 2004). Proper and timely diagnosis is therefore critical in helping reduce morbidity and mortality associated with jaundice. However, differential diagnosis of jaundice has been found to be a clinical challenge that often employs the use of clinical, laboratory and imaging findings. Ultrasound remains the initial imaging modality of choice in these patients, and it relies heavily on laboratory correlation. However overlap among the traditionally used laboratory parameters has been reported, hence posing a diagnostic dilemma (Kumar and Bhatia 2011, Saboo, Vijaykumar et al. 2012).

1.3 Study Justification

Literature shows variation in serum liver enzymes in the setting of different liver pathologies (Thapa and Walia 2007). However, no study has been done locally to demonstrate how different serum liver enzymes vary with different hepatobiliary ultrasound findings, a pattern that is key in evaluation of patients with jaundice. Furthermore, one study has attempted to show the usefulness of the ALT/ALP ratio, also known as the R-value, in predicting hepatobiliary ultrasound outcomes (Yu, Fu et al. 2012). This too has not been studied locally, yet we know that significant enzymatic variations do exist in different populations living in different environmental conditions (Rahmioglu, Andrew et al. 2009).

This study therefore aims to determine the correlation between hepatobiliary ultrasound findings with the traditionally used serum liver enzymes as well as the relatively new R-value. It is hoped that the findings of this study will help clear the existing confusion on enzyme overlap and perhaps help introduce the R-value into the differentiation of general hepatocellular and obstructive jaundice.

1.4 Research Questions

This study sought to answer the following questions:

1. What are the ultrasound findings in the hepatobiliary system of adult patients with jaundice at MTRH?
2. What is the correlation between the hepatobiliary ultrasound findings and serum liver enzymes in adult patients with jaundice at MTRH?

1.5 Research Objectives

1.5.1 Broad Objective

To describe the hepatobiliary ultrasound findings and determine their correlation with serum liver enzymes among adult patients with jaundice at MTRH.

1.5.2 Specific Objectives

- To describe the hepatobiliary ultrasound findings in adult patients with jaundice at MTRH.
- To determine the correlation between hepatobiliary ultrasound findings with serum liver enzymes among adult patients with jaundice at MTRH

CHAPTER TWO: LITERATURE REVIEW

2.1 Epidemiology

The different types of jaundice are thought to vary in incidence from population to population. Gracanin AG et al, in his study on Etiology and epidemiology of obstructive jaundice in Continental Croatia, found obstructive jaundice to be a disease of the elderly population. He found that the frequency of illness was higher among female population, and the most frequent cause of obstructive jaundice was gallstones (54.1% of patients) (Gudelj Gracanin, Kujundzic et al. 2013).

A retrospective study of 250 HIV positive patients in Thai found 10.4% to be jaundiced. Alcoholic liver disease was the most common cause of jaundice (42.31%), followed by opportunistic infections (34.62%). Neoplasms were found to be the cause of jaundice in 3 patients (11.54%), while drug-induced hepatitis and viral hepatitis B was identified as the cause of jaundice in 2 patients (7.69 percent) and patient 1 (3.84 percent), respectively. Jaundice was found to be common among patients with advanced state of HIV infection than patients in early stage (V Wiwanitkit 2004)

2.2 Aetiology

The presence of jaundice is usually, but not always a sign of liver disease. The causes of jaundice are many. Geo-cultural factors influence the prevalence of liver disease of public health importance in any country, and so liver disease may vary from country to country and in the same country in different cultural groups and at different periods of time. The commonest causes of chronic liver diseases all over the world are infection with hepatitis B virus, hepatitis C virus and alcohol abuse. However, in South-eastern Asia, the commonest causes encountered are infective hepatitis, obstruction to bile ducts by gall stones or tumours, alcoholic liver disease, and drugs (Islam 2012).

In Netherlands, a study of 702 patients presenting with jaundice over a two year period found 20% of the cases to be due to pancreatic or biliary carcinoma, 13% due to gall stones, and 10% due to alcoholic liver (Reisman, Gips et al. 1995). Forty per cent of cases of jaundice in the US are due to biliary obstruction (Corsetti JP 1991).

In terms of non-obstructive jaundice, a retrospective study of over 700 patients at Wishard Memorial Hospital, Indiana**,** reported 22% to be due to sepsis or ischemic liver injury, 13% due to non-alcoholic liver disease, 9% due to acute viral hepatitis, and 4% due to drug-induced liver injury (Vuppalanchi, Liangpunsakul et al. 2007).

A study in Sudan to assess the role of ultrasound in diagnosis of patients with obstructive jaundice showed the following as the causes of obstructive jaundice: gallstones 19%, mass 51%. This study further demonstrated that sensitivity of ultrasound in determining the level of obstruction was 96%. The prevalence of obstructive jaundice was found to be higher in females (58%) than in males (42%). The study found that obstructive jaundice

constituted 89.2% and non-obstructive jaundice 10.8% of the cases of jaundice (Moawia Gamersddin 2013).

In Kenya, Ngure John Githuku in his thesis work studied 165 patients with jaundice at Kenyatta National Hospital (KNH) using ultrasound and found the following: normal findings (27), hepatitis (19), metastasis (14), hepatocellular carcinoma (8), liver cirrhosis (12), pancreatic carcinoma (15), gallstones (7), fatty liver (9), gallbladder carcinoma (8) and indeterminate (12). Laboratory tests 27 were positive for hepatitis B and 3 for hepatitis C. HIV positive patients were 24 (14.5%). Differentiation of obstructive from non-obstructive jaundice was achieved in 93% of the cases. The myriad causes of diffuse liver disease were not accurately differentiated. In obstructive jaundice, the cause and site of obstruction was not accurately determined by ultrasound (Githuku 2009).

Still in Kenya, a study done by Ngoseywe at Kenyatta National Hospital to determine the ability of ultrasound to accurately determine the site and cause of the obstruction gave the following results: The site of obstruction was predicted in 26 patients (sensitivity of 65% and specificity of 77%), but was indeterminate in 35% because of the inability to visualize the complete biliary tract. The cause of obstruction was correctly predicted in 31 patients (sensitivity of 78% and specificity of 72%) and was indeterminate in 22%. He found that Ultrasonography was accurate in differentiating obstructive from non-obstructive jaundice but was nonspecific in assigning a definite cause of obstruction and in predicting the site of obstruction (Ngoseywe 2008).

2.3 Evaluation of the Jaundiced Patient

Clinical symptoms and physical examination are often not enough for definite diagnosis of patients with jaundice. Ultrasound together with biochemical tests remain invaluable tools in determining the nature of the hepatobiliary pathologies and therefore helping set the direction of treatment.

2.3.1 Laboratory Evaluation of the Jaundiced Patient

Blood biochemistry is useful in establishing the presence of abnormal liver function tests and evaluating the bilirubin level. Although it is said to be possible to try and establish whether a patient presenting with jaundice has a pre-hepatic, hepatic or post-hepatic abnormality from the type of bilirubin elevation in the blood, in majority of patients there is a mixed picture with elevation of both conjugated and unconjugated bilirubin. By assessing these biochemical parameters, the potential cause of jaundice can fall into one of two categories:

1. Obstructive (usually post-hepatic), where the drainage of bile is impeded.

2. Non-obstructive (pre-hepatic and hepatic), where there is excessive haemolysis or disturbance in hepatic parenchymal function.

The clinical approach to investigating the jaundiced patient is based on two main biochemical factors. If bilirubin is absent in the urine, the reasons are due to a non-obstructive cause and radiological imaging has a limited role. If present in the urine, then the cause is likely to be owing to obstruction of the excretion of bile from the normal route and radiological imaging plays a crucial/ role in the evaluation.

The second factor depends on the liver function tests. Liver function tests are groups of blood tests which are used to give information on the state of a patient's liver (Lee 2009). These tests have been classified into:

a) Tests of the liver's capacity to transport organic anions and to metabolize drugs- these include serum bilirubin, urine bilirubin and urobilinogens.
b) Tests that detect injury to the hepatocytes (liver cells) also referred to as serum liver enzyme tests- These include serum aminotransferases (Alanine Aminotransferase, Aspartate aminotransferase), Alkaline phosphatase, Gamma glutamyl transpeptidase and 5 nucleotidase.
c) Tests that assess the liver's biosynthetic capacity- These include serum proteins, albumin, prealbumin, serum ceruloplasmin, prothrombin time etc.

Of the mentioned tests, the most commonly used LFTs include serum bilirubin levels (both total and direct), serum albumin, Serum aminotransferases, alkaline phosphatase and gamma glutamyl-transpeptidase.

Bilirubin is an endogeneous anion derived from the degradation of red blood cells. When the LFTs are abnormal and serum bilirubin levels more than 17micromols per litre, an underlying liver disease is suggested. Bilirubin is divided into total, direct (conjugated) and indirect (unconjugated) bilirubin. The normal range for total bilirubin is 0.2-0.9mg/dl (2-15micromols per litre). It is slightly higher by 3-4micromols per litre in males compared to females.

The serum aminotransferases (ALT and AST) are the most frequently used and specific indicators of hepatocellular necrosis. ALT is primarily localized in the liver but AST is

present in a wide variety of tissues including the heart, skeletal muscle, kidneys, brain and liver.

Severe elevations of aminotransferases (>20 times, 1000u/l) are seen in severe viral hepatitis, drug or toxin induced hepatic necrosis and circulatory shock.

Moderate elevation of aminotransferases (>3-20 times) is seen in acute hepatitis, neonatal hepatitis, chronic hepatitis, autoimmune hepatitis, drug induced hepatitis, alcoholic hepatitis and acute biliary obstructions. The ALT is usually more frequently increased compared to AST except in chronic liver disease.

Mild elevation of aminotransferases (1-3 times) is seen in sepsis induced neonatal hepatitis, fatty liver, extrahepatic biliary atresia, cirrhosis, non-alcoholic steatohepatitis (NASH), drug toxicity, myosistis, duchenne muscular dystrophy and after vigorous exercise (Daniel and Marshall 1999). One third to one half of healthy individuals with an isolated elevation of ALT on repeated testing have been found to be normal (Daniel and Marshall 1999).

The AST/ALT ratio is useful in Wilson's disease, CLD and alcoholic liver disease and a ratio of more than 2 is usually observed. The absence of ALT rise is probably due to pyridoxine deficiency. In NASH, the ratio is less than 1 in the absence of fibrosis on liver biopsy (Friedman 2003).

In viral hepatitis, the ratio is usually less than one and invariably rises to more than one as cirrhosis develops possibly due to reduced plasma clearance of AST as a result of impaired function of sinusoidal cells. ALT exceeds AST in toxic hepatitis, viral hepatitis, chronic active hepatitis and cholestatic hepatitis.

Alkaline phosphatases are a family of zinc metaloenzymes present in nearly all tissues. Alkaline phosphatase from the liver, bone and kidney are thought to be from the same gene but that from the intestine and placenta are derived from different genes. In healthy people, most circulating ALP originates from liver or bone. Average values of serum ALP vary with age and are relatively high in childhood and puberty and lower in middle age and higher again in old age. Males usually have higher values than females. Levels correlate with a person's weight and inversely with the person's height. Isolated cases of ALP in otherwise healthy individuals often return to normal on follow up. Highest levels of ALP occur in cholestatic disorders.

Gamma glutamyl-transpeptidase (GGT) is found in large amounts in the kidneys, pancreas, liver, intestine and prostate. The levels of GGT are high in neonates and infants and also increase after 60years of life. Men have higher values. Children more than 4years have serum values of normal adults. The normal range is 0-30IU/litre. GGT may reach peak levels in the second to third week during acute viral infections and in some patients the levels remain elevated for 6weeks. Measurement of GGT levels is useful in differentiating between bony disorders and liver disease in the background of elevated ALP since GGT is only raised in cholestatic conditions and not bony disorders (Rosalki SB 1999).

Other conditions in which GGT may be elevated include uncomplicated Diabetes Mellitus, acute pancreatitis and myocardial infarction. GGT levels may also rise with the use of drugs like phenobarbitone, phenytoin and paracetamol. GGT may also rise in Guillaine Barre syndrome, hyperthyroidism, and obesity.

The above liver function tests have traditionally been used in the differential diagnosis of jaundice. The obstructive pattern of jaundice has been associated with increased Bilirubin, ALP and GGT. The hepatocellular pattern on the other hand has long been associated with increased Bilirubin, AST, and ALT.

However, overlaps in the elevated bilirubin and serum enzymes have been reported. Hepatitis A infection for instance, may present a cholestatic picture with marked and prolonged elevation of ALP (Rosalki SB 1999).

The R-value

Biochemical tests including Direct Bilirubin/Total Bilirubin (DBIL/TBIL), hereinafter referred to as D/T have been used as one of the important indicators of differentiating the different types of jaundice. This is combined with serum liver enzyme changes to search for the causes of jaundice. However, in trying to differentiate between obstructive (cholestatic) and hepatocellular jaundice, there are often overlaps in the types of elevated bilirubin and serum enzymes making the distinction difficult (Rosalki SB 1999).

The ALT/ALP Ratio (referred to as the R-value) was formulated by the Medical Science International Organizing Committee to which the World Health Organization belongs to help in differentiating the types of acute drug induced acute liver damage into liver cell type, intrahepatic cholestatic type or the mixed type.

In one of the initial studies to assess the role of the R-value in the differential diagnosis of jaundice, Yu et al in China studied 336 cases of patients with jaundice and recorded their ALT, ALP, DBIL and TBIL to calculate their R-values and D/T values. The R-values and D/T values were then compared between cholestatic and hepatocellular jaundice. It was found that the R-value for the positive rate of diagnosis of hepatocellular jaundice was

34.9% and D/T value was 16.1%, with R>D/T (P<0.05). However, it was found that for obstructive (cholestatic) jaundice, the D/T values for positive diagnostic rate was 93.0%, and the R-value 75.4%, with D/T>R (p<0.05). It was concluded that for the positive rate of diagnosis of hepatocellular jaundice, the R-value was higher than D/T, while D/T was better than the R-value for the positive rate of diagnosis of obstructive jaundice (Yu, Fu et al. 2012).

In this study, we attempt to give an assessment of the association of the R value with the two types of jaundice as seen on ultrasound and hopefully help introduce the R value into the differential diagnosis of general hepatocellular jaundice and obstructive jaundice. We hope to provide one of the initial assessments of R value in the differential diagnosis for both categories of jaundices.

2.3.2 Hepatobiliary Ultrasound Examination

In a jaundiced patient with normal liver biochemistry the causes are likely to be pre-hepatic and imaging is not routinely indicated. If the liver function tests are abnormal, radiological imaging is appropriate to evaluate the liver parenchyma and bile ducts (RUDRALINGAM and Sukumar 2013).

Based on clinical history, physical examination and blood biochemistry alone, it is often impossible to accurately distinguish between an obstructive (cholestatic) and a non-obstructive cause of jaundice, thus radiological evaluation is essential. The primary aims of radiology are to assess whether the cause of jaundice is obstructive and to determine the cause of obstruction when present (RUDRALINGAM and Sukumar 2013).

As a solid organ, the liver is particularly suitable for ultrasound examination and it is seldom covered by gas-containing bowel. Its smooth contour and soft structure can be appreciated as it moves up and down with breathing. The liver is used as an acoustic window for visualization of other structures, including the right kidney and adrenal gland, the gallbladder and the pancreas. Vessels and bile ducts of the liver are particularly well seen on ultrasound studies. Blood flow can be studied using colour flow Doppler, and the direction and velocity of flow in the portal vein can be evaluated with pulsed wave Doppler (Stephanie Ryan 2004).

Examination Criteria

An acronym has shown to be didactically helpful [“SSOTM”]:

- S = size
- S = shape
- O = outline
- T = texture
- M = measurement

Size

The size of the liver has been measured by many methods, including 3D-reconstructions. Liver size measurement has been found to have no impact in daily routine because there is no reliable and reproducible ultrasound method established so far.

Shape

Normally described as pyramidal.

Outline

The normal liver surface should be smooth with no lumps protruding or indentations. The inferior liver border in the normal patient should have an acute angled edge.

Texture, echogenicity

The normal liver parenchyma is of medium homogenous echogenicity, usually slightly darker than the spleen and slightly brighter than the renal cortex independently of the age except in childhood. It is essential when comparing the liver with the spleen and renal cortex that the comparison is done at the same depth. Liver surface and vessels borders are smooth and vascular architecture with its classic dichotomy in branching is percepted as a harmonic and detailed aspect. The image of the normal parenchyma varies very little among individuals.

Liver veins

The three liver veins are positioned in between the liver segments. Their course - additionally to the Glisson`s triad - is helpful in defining liver lobes and liver segments. Number and course of liver veins is somewhat variable.

Portal vein

Formed by the confluence of the splenic and superior mesenteric vein, the portal vein can be sonographically displayed using scans more or less perpendicular to the lower costal margin (orientation might be achieved referring from the right shoulder to the umbilicus), preferably in a left decubitus position and in variably deep inspiration. Inside the liver, the portal vein bifurcates into a main left and right branch. The first (right) portal vein branch splits into an anterior and into a posterior branch, which itself leads to the segments V – VIII. The latter (left) main portal branch bifurcates into segments II and III

and, additionally, into the left medial branches for segments I (caudate lobe), IVa and IVb.

Hepatic artery

The common hepatic artery has its source from the celiac axis, branching into the gastroduodenal artery and into the proper hepatic artery (arteria hepatica propria). Anatomical variations are frequent (in up to 50 %), e.g. the origin of the left proper hepatic artery out of the left gastric artery as well as the variable arterial supply of the liver by superior mesenteric artery branches. The hepatic artery runs with the portal vein, the right main arterial branch frequently meandering around the portal vein sonographically displayed in short segments medially (or less often laterally) of the portal vein.

Bile ducts

Bile ducts accompany the portal vein and hepatic artery branches from the liver hilum into the liver lobules, intrahepatically forming the ductus principalis dexter and the ductus principalis sinister, which join as common bile duct (CBD). The extrahepatic course of the CBD is cranially (pre-pancreatic) often ventral to the portal vein and caudally (intrapancreatic) more dorsolateral. The respective course of the hepatic artery is more variable.

The CBD, and therefore, the liver hilum, is often best examined in a left lateral decubitus position using a subcostal approach in slight inspiration (Dietrich, Serra et al. 2010).

2.4 Ultrasound Findings in Hepatobiliary Diseases

Jaundice may be caused by hepatic parenchymal disease, obstruction of the bile ducts or may be prehepatic with each of these different hepatobiliary diseases producing different ultrasound findings.

2.4.1 Hepatic steatosis (fatty liver):

Is the most common liver pathology. Ultrasound has been found to be very accurate and reliable in the detection of fatty liver, compared to histology, with sensitivities of up to 90% and specificities of up to 97% being reported (Hernaez, Lazo et al. 2011). In transabdominal hepatobiliary ultrasound, hepatic steatosis is characterized by increased echogenicity, in comparison to splenic or renal parenchyma at the same depth. Other sonographic signs of hepatic steatosis include decreased detail display of intrahepatic vasculature and hepatomegaly with rounded borders (Dietrich, Serra et al. 2010).

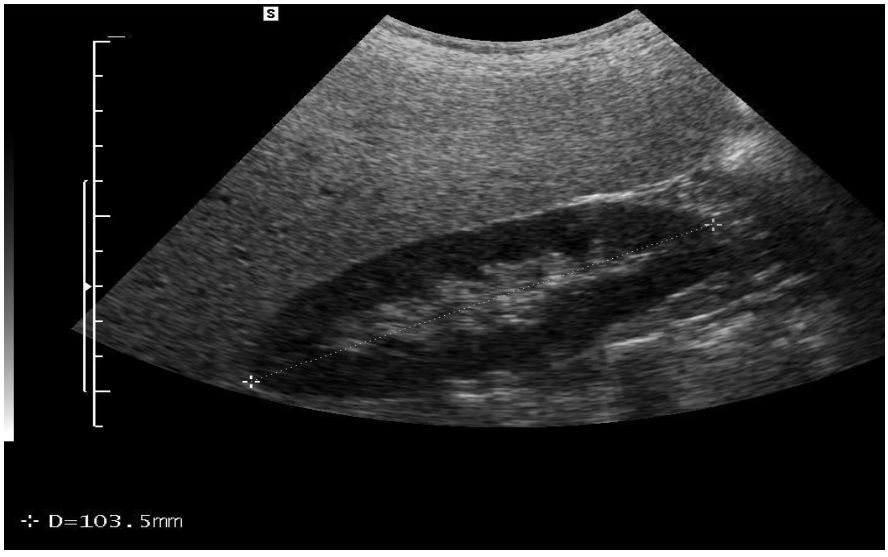


Figure 2: Sonographic signs of hepatic steatosis (fatty liver) include hepatomegaly with rounded borders, increased echogenicity and decreased detail display of intrahepatic vascular architecture. There is an exaggeration of the difference between the renal and hepatic parenchyma. The right kidney is shown between callipers (+)

2.4.2 Liver cirrhosis/ fibrosis:

The sensitivity of ultrasound in detecting moderate liver fibrosis and established cirrhosis has been reported to reach 100%, with a specificity of 89% for fibrous tissue (Joseph, Saverymuttu et al. 1991). Therefore, ultrasound can provide a non-invasive prediction of liver histology which in moderate fibrosis and established cirrhosis can both be highly sensitive and specific. Typical signs of liver cirrhosis include inhomogeneous echo-pattern, and irregular liver surface. Sometimes distinctive nodules may be noted. In the early stages, the liver is enlarged while in late stages of cirrhosis, the liver shrinks significantly. Disproportionate segmental atrophy and hypertrophy are also typical (Dietrich, Serra et al. 2010).

2.4.3 Acute Inflammatory Conditions of the Liver (Acute hepatitis)

In patients with hepatitis, two distinct patterns have been reported. In acute hepatitis, the predominant findings are accentuated brightness and more extensive demonstration of the portal vein radicle walls and overall decreased echogenicity of the liver. Chronic hepatitis primarily reveals decreased brightness and number of portal vein radicle walls and overall increased liver echogenicity (Kurtz, Rubin et al. 1980). However difficulties in differentiating a normal liver from a hepatitis liver have been reported in some cases due to absence of parenchymal liver changes (Gosink, Lemon et al. 1979).

2.4.4 Focal Liver Lesions

A focal liver lesion is defined as the difference in echogenicity between a circumscribed area and the surrounding liver tissue. Focal liver lesions are characterized by the location, number size, shape, boundary, echogenicity and vascularity. These lesions can be

categorized as benign and malignant lesions. Conventional B-mode ultrasound unequivocally detects typical liver cysts and calcifications. Detection and characterization of liver tumors is however still a challenge.

Liver cysts are common and are easily diagnosed using conventional B-mode ultrasound. They are characterized as round, anechoic smoothly delineated structures with posterior acoustic enhancement. These are referred to as typical cysts whereas cysts with only some of these features are referred to as atypical.

Calcifications are seen as hyperechoic structures normally with posterior acoustic shadowing.

Liver hemangiomas are the most common benign liver tumors. Over 90% of hemangiomas can be reliably diagnosed using imaging methods. Most of these lesions have typical conventional B-mode ultrasound features. They are characterized as hyperechoic lesions, less than 3cm in diameter, lobulated with well-defined outline, located to adjacent liver vessels. Colour Doppler often detects little or no blood flow inside owing to slow flow velocity inside the capillary hemangioma. One can possibly detect feeding and draining vessels and there is usually absence of any signs of invasive growth.

Small hepatocellular carcinoma lesions may have a wide range of appearance and may show increased or decreased echogenicity in relation to the adjacent normal liver parenchyma. In a retrospective study of 35 cases of histopathologically proven and ultrasonographically suggested cases of hepatocellular carcinoma, it was found that hepatocellular carcinoma showed hyperechoic pattern in 22 cases (63%), hypoechoic

pattern in 2 cases (6%), and mixed pattern in 11 cases (31%). The margin of tumor was ill-defined in 19 cases (54%) and well defined in16 cases (46%). The size of tumor by sonographic measurement was larger than 5 cm in diameter in 33 cases (94%). The number of tumor was solitary in 19 cases and multiple in 16 cases. The sites of involved lobe were right lobe in 22 cases (63%), left lobe in 2 cases (6%), and both lobes in 11 cases (31%). Associated sonographic findings were hepatomegaly with focal contour change in 25 cases (71%), splenomegaly in 16 cases (46%), cirrhosis of liver in 15 cases (43%), ascites in 11 cases (31%) and tumoral thrombosis in portal vein in 8 cases (23%). The sex ratio was 6 : 1 male predominance and the age ranges from 32 to 76 years with highest incidence in 5th and 6th decades (Ryu, Woo et al. 1983).

In a prospective study to evaluate primary and secondary signs of acute cholecystitis using ultrasound, It was found that real time sonography alone, combined with both primary and secondary signs can be predictive in 80% of patients with suspected cholecystitis (Ralls, Colletti et al. 1985).

2.4.5 Pancreatic Masses

Studies have reported varied features of pancreatic head masses. Pancreatic masses associated with jaundice are almost invariably located in the pancreatic head. In his study, Yassa et al found 80% of pancreatic masses to measure 4.5x 3.5cm on average, 55% to be hypoechoic, 45% heterogeneous, 60% ovoid/spherical. He also found peripheral vascular encasement in 45% of cases (Yassa, Yang et al. 1997). He however

found only 69% of the tumors to be in the pancreatic head with rest located in the body and tail.

2.4.6 Gall Bladder Masses

Varying features of gall bladder masses on ultrasound have been documented. Rooholamini et al reviewed 59 cases of histologically proven carcinoma of the gall bladder and found the following: Radiologic findings included focal or diffuse thickening of the gallbladder wall (49%), a mass in the gallbladder fossa (37%), and an intraluminal mass (14%). Associated findings were cholelithiasis (64%), biliary duct dilatation (38%), invasion of the adjacent structures (67%), distant metastases other than those of the liver (3%), and porcelain gallbladder (4%) (Rooholamini, Tehrani et al. 1994).

In another study, analysis of clinical features and imaging features in patients subjected to surgery for gallbladder neoplasm in the Reina Sofía General University Hospital (Murcia) during the period of 2000–2011 was done. Results: A total of 15 cases of gallbladder cancer were found during the study period. The ultrasound findings showed gallbladder wall thickening (>4 mm) in 8 cases, intraluminal mass in 4 cases, scleroatrophic gallbladder in 2 cases, and a mass replacing the gallbladder in one case (Maldonado, Lopez et al. 2014).

Githuku in his study at Kenyatta National Hospital found that the most common pattern of gall bladder cancer was that of a mass engulfing the gallbladder fossa or a localized gallbladder wall thickening (Githuku 2009)

2.4.7 Biliary Obstruction

Ultrasound is approximately 90% accurate in differentiating obstructive (cholestatic) from non-obstructive jaundice by depicting presence of biliary dilatation. Ultrasound accurately determines the level of obstruction in 92-95% of the cases and the cause of obstruction in 71-88% of the cases (Brant). Biliary obstruction is demonstrated by presence of dilated biliary ducts on ultrasound.

CHAPTER THREE: METHODOLOGY

3.1 Study Design

This was an analytical cross-sectional study.

3.2 Study Site

The study was carried out at the Radiology and Imaging department of Moi Teaching and Referral Hospital (MTRH). The Hospital is within Eldoret town, Uasin Gishu County, which is 350 Kilometers North West of Nairobi. MTRH is a level 6 health facility serving as a teaching hospital for Moi University School of Medicine, Nursing, Public Health and Dentistry. Other institutions that utilize this facility include Kenya Medical Training Center (KMTC), Eldoret and University of Eastern Africa Baraton School of Nursing. MTRH is also a training center for medical, clinical and nursing officer interns as well as for doctors pursuing specialist training. It serves as the main referral hospital for the Western part of Kenya and North rift and has a catchment population of approximately 13 million people.

3.3 Study Population

The study population was patients aged 18 years and above, presenting with jaundice at MTRH and referred for hepatobiliary ultrasound.

3.4 Eligibility criteria

3.4.1 Inclusion Criteria

1. Adult patients (18 years and above), with jaundice referred for ultrasound
2. Have the biochemical test results (ALT, ALP, AST, GGT, Bilirubin).

3.4.2 Exclusion Criteria

1. History of previous hepatobiliary surgery
2. Patients without a detectable increase in serum levels of any of the following: ALT, AST, GGT, ALP and Bilirubin.

3.5 Sampling Techniques

Census study was preferred in this study based on the few cases of adult patients with jaundice referred for hepatobiliary ultrasound at MTRH. Data for 2014 showed that 100 gadult patients were sonographically evaluated for jaundice. All adult patients presenting with jaundice and referred for hepatobiliary ultrasound during the study period were therefore consecutively sampled into the study. A total of 79 patients were enrolled in the study.

3.6 Study Procedure

Figure 3 below shows the study recruitment schema. Patients with jaundice (from examination by the referring clinician) presenting for hepatobiliary ultrasound were scanned. Verbal consent was obtained to review their biochemistry laboratory results if they already had them. If they had the laboratory results and they met the inclusion criteria, a written consent was sought for inclusion into the study. Verbal consent was sought from potential study patients who did not have Liver function test results at the time of the ultrasound examination for follow up and review of laboratory results. If the laboratory results were found, a written consent for inclusion into the study was obtained.

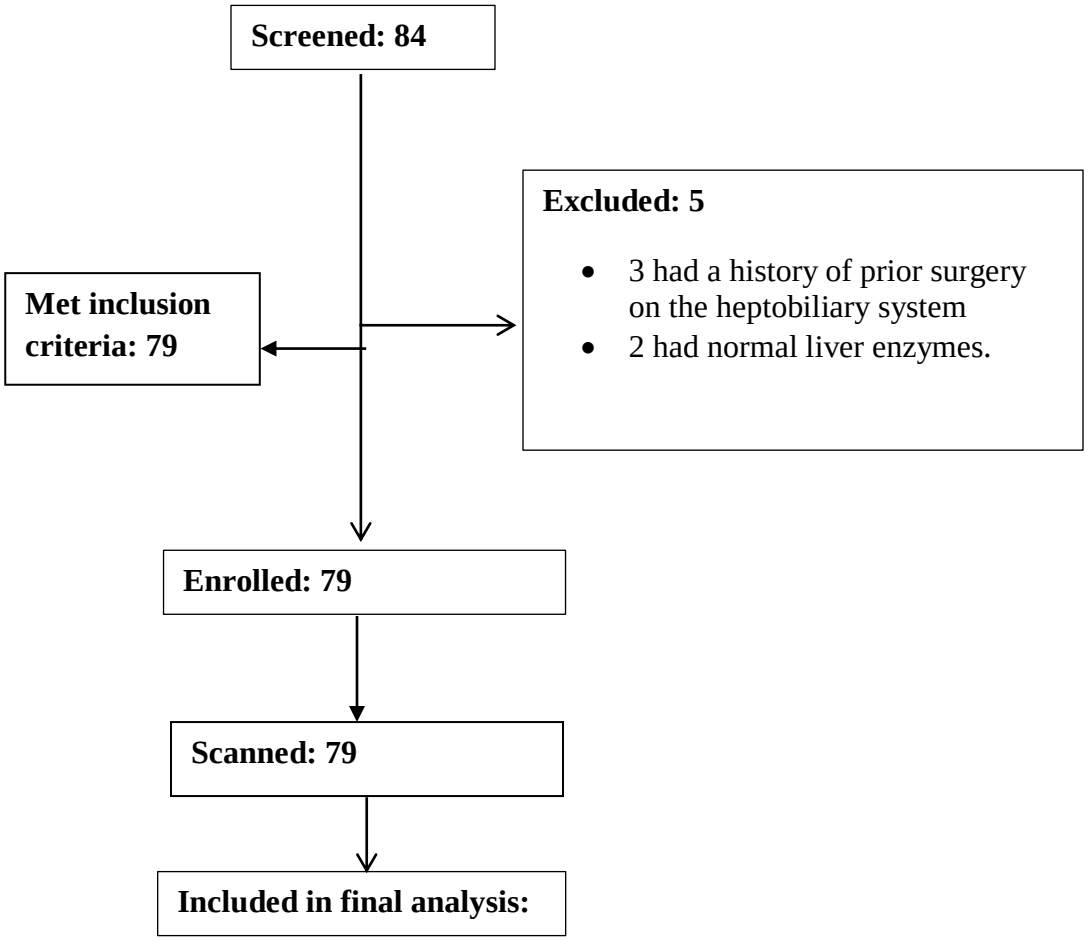


Figure 3: Enrolment flow Chart

3.7 Sonographic Examination Procedure

All the examinations were performed by the principal investigator or by a trained assistant on duty using Philips HD11 XE machine model 2006 with 3.5MHz curvilinear transducer with Colour Doppler capability. Pre-warmed coupling gel was applied to the transducer. US examination was aimed at localizing the pathologic lesion within the liver, gall bladder, pancreas or surrounding organs causing jaundice, characterizing the lesions

in terms of echo-texture, definition of outline, determination of the size and extent of the lesion. Transverse and longitudinal side-by-side images of both the liver/spleen and liver/right kidney were obtained and documented for comparison.

Data was captured in the form of hard copy sonograms. Images were also saved in the ultrasound machine computer memory and compact disks. Image interpretation was done by the principal investigator and later reviewed by two independent consultant radiologists. The abnormalities detected were described and a diagnosis made on basis of characteristic sonographic appearances. Standard definitions of ultrasound pathology were used. The causes of jaundice as found on ultrasound were then categorized as: (i) obstructive, (ii) hepatocellular or (iii) others, where "others" included normal findings, indeterminate findings or mixed obstructive/hepatocellualr findings. Correlations were then made between obstructive and hepatocellular groups with serum aminotransferases (Alanine aminotransferase-ALT, Aspartate aminotransferase-AST), Alkaline phosphatase (ALP), Gamma glutamyl transpeptidase (GGT), ALT/ALP ratio (R-value), AST/ALT ratio, and Direct/Total bilirubin (D/T) ratio. All the laboratory tests were done in the main MTRH laboratory for standardization. The acceptable time frame between laboratory investigation and ultrasound examination was within 24hours.

Data analysis was done using STATA version 13E software in accordance with the set objectives.

The socio-demographic and radiological data was entered in a data sheet. The data tools were kept in a secured cabinet during the study period to ensure no access by unauthorized persons.

3.8 Data Collection and Management

3.8.1 Data Collection

Data was collected between October 2015 and November 2016. Entry was made in the questionnaires and later transferred to a computer database. Double entry was used to ensure accuracy of the data. All patient details were kept confidential and data was only available to the investigator and the supervisors via password access. Patients were given a copy of their results and had autonomy over who else could view their scan result(s). Serial numbers were used to protect patients' identity. At the end of each day data collection forms were verified for completeness and coded.

3.8.2 Quality Control

All US scans were done at MTRH US room that has internal quality controls. The machine used in all patients was the Phillips HD11 XE. The scans were performed by the Principal Investigator conducting the study plus two other trained assistants based on standardized evaluation criteria. Images were then reviewed by two consultant radiologists. All laboratory tests were done at the MTRH main biochemistry laboratory which has internal quality controls for purposes of standardization.

3.8.3 Data Analysis and Presentation

Data analysis was conducted using STATA version 13 SE. Categorical variables such as gender and the level of education among others were summarized as frequencies and the corresponding percentages. Continuous variables such as age were summarized as median and the corresponding inter-quartile ranges since they did not assume normal distribution. Comparison of the continuous variables was done using nonparametric two

sample Wilcoxon rank sum test. Correlation between continuous variables was done using the Spearman rank correlation. Results were presented using tables and charts.

3.9 Ethical Considerations

Approval to carry out the study was sought from the Institutional Research and Ethics Committee (IREC) and the Director of Moi Teaching and Referral Hospital. Informed consent was sought from patients/guardians. All patients/guardians were informed about the study and the procedures involved in the study and the possible benefits and harm to them and that the procedure was generally safe but had potential risks. Regarding the necessity of the investigation for management of the patient, consent was sought from the hospital management and IREC to allow studying of the sonograms and laboratory findings of the patients who had undergone evaluation. All patients received medical attention as necessary regardless of whether they did or did not consent to participate in the study. No incentives or inducements were used to lure patients to participate in the study. Patients were informed of their results and appropriate standard treatment given. Confidentiality was maintained throughout the study. The data collection forms used neither contained the names of the patients nor their personal identification numbers. Data collecting material were kept in a locked cabinet during the study period. The results of the research will be presented to the Hospital's management and the university's department of Radiology and Imaging for use as necessary. It will also be available for academic reference in the College of Health Sciences Resource Centre. The results of this research shall be availed for publication in a reputable journal of medicine for use by the wider population in the general improvement of patient management and as a reference for future studies.

CHAPTER FOUR: RESULTS

4.1 Demographics of the Participants

A total of 84 participants were screened for eligibility into the study. Of these, 79 were successfully consented and enrolled. The remaining 5 were excluded for various reasons as shown in **figure 3.**

Among the 79 participants included in the final analysis, 48% were male, median age 34 years (IQR 22-50). As illustrated in **figure 4**, majority (69%) were residents of Uasin Gishu County. Other social-demographic characteristics are shown in **Table 1.**

Table 1: Social-demographic characteristics of participants

Variable	Median (IQR); n(%)
Age (years)	34 (22-50)
Gender	79
Male	38 (48%)
Female	41 (52%)
Education	79
None	2 (2%)
Primary	11 (14%)
Secondary	41 (52%)
Tertiary	25 (32%)

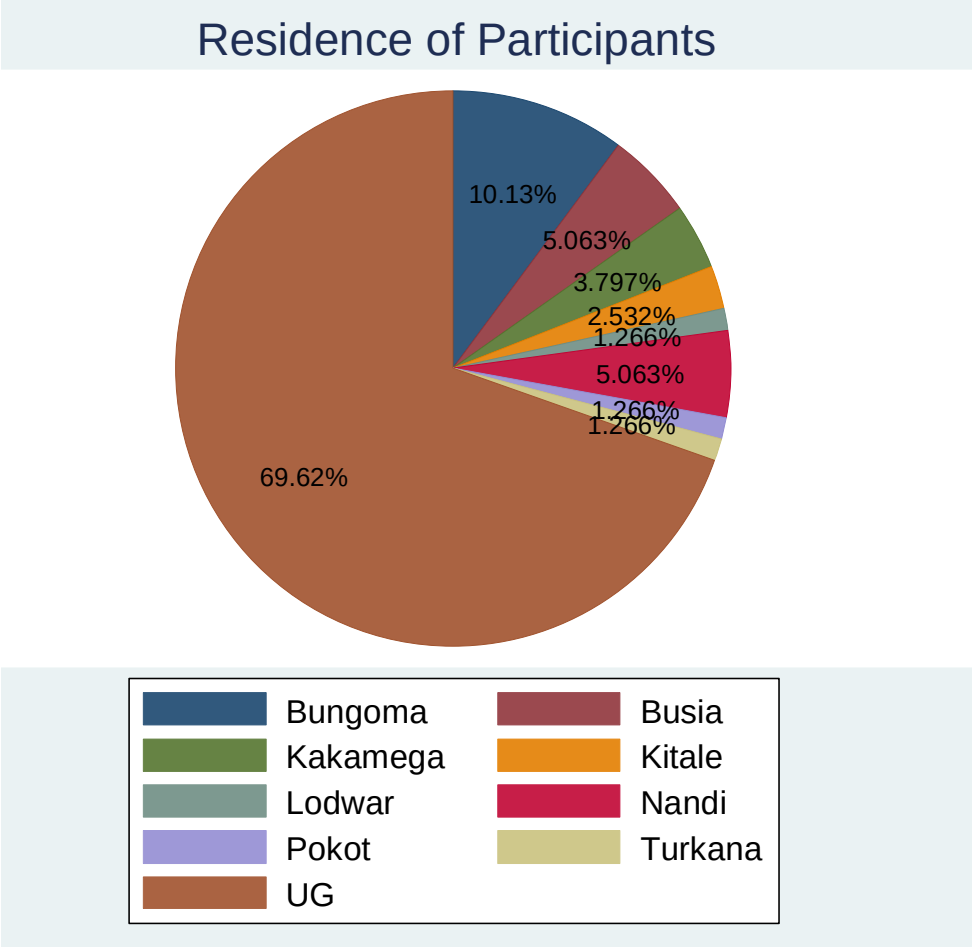


Figure 4: Pie chart showing place of residence of participants

4.2 Clinical Characteristics of the Participants:

The clinical characteristics of the study participants are summarized in **Table 2.** As illustrated, the median duration of jaundice before undergoing ultrasound examination was 14 days. Majority of the participants (>90%) did not report any history of yellow eyes in the past. Nearly all the participants reported having dark urine.

Table 2: Summary of Clinical Characteristics

Variable	Median (IQR); n (%)
Duration of Jaundice (Days)	14 (5-30)
History of yellow eyes in the past	79
Yes	5 (6%)
No	74 (94%)
Dark Urine	79
Yes	76 (96%)
No	3 (4%)
Yellow Urine	79
Yes	2 (3%)
No	77 (97%)
Pruritus	79
Yes	25 (32%)
No	54 (68%)
Liver span	79
Average	69 (87%)
Increased	3 (4%)
Reduced	7 (9%)

4.3 Causes of jaundice as determined by ultrasound:

Overall, the most common cause of jaundice as determined by ultrasound was attributed to acute inflammation of the liver (38%). Pancreatic head mass constituted 11%, cholecystitis 11%, liver fibrosis/cirrhosis 10%, gall stones 6%, fatty liver 5%, liver mass 4% and liver cyst 1%. In 13% of the participants no hepatobiliary abnormality was detected on ultrasound despite the presence of jaundice and abnormal liver function tests.

4.3 Distribution of jaundice by ultrasound disease pattern:

Figure 5 shows the proportions of category of jaundice as determined ultrasonographically. 56% of the participants had hepatocellular type of jaundice and 31% had obstructive type of jaundice as determined by ultrasound. 13% had normal, indeterminate or mixed findings categorized as "others."

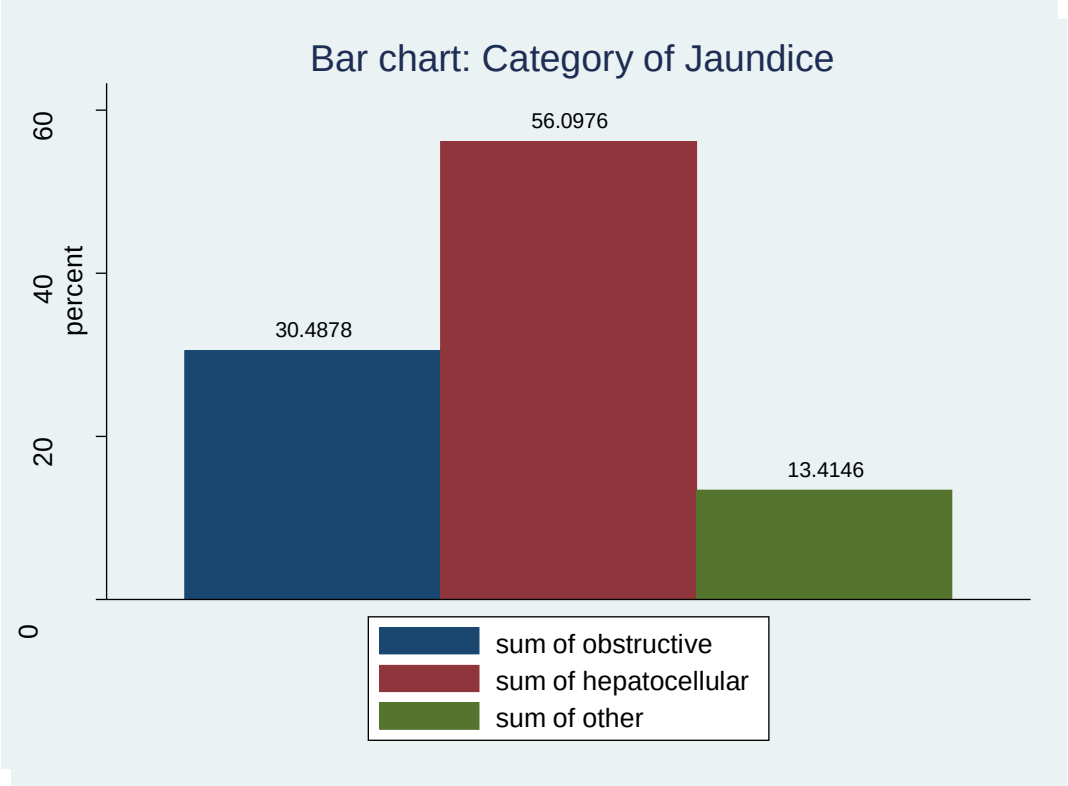


Figure 5: Bar Chart Showing Category of Jaundice

4.4 Distribution of Obstructive Cases as per Gender

Nine patients had pancreatic head masses, of which 6 were males and 3 were females. In patients with gall stone, 4 were females while 2 were males. Gallbladder masses had an equal distribution with 2 males and 2 females. Cholecystitis had 5males and 4 females.

Table 3: distribution of obstructive jaundice as per gender

Obstructive	Gender	
	M	**F**
Pancreatic head mass	**6**	**3**
Gall stones	**2**	**4**
Cholecystitis	**5**	**4**
Gall bladder mass	**2**	**2**

4.5 Distribution of Hepatocellular Cases as per Gender

Majority of patients had hepatocellular jaundice with the females constituting 53%. There was an almost equal gender distribution for acute inflammatory conditions and fatty liver with 16 males against 14 females for acute inflammatory liver conditions and 2 males against 3 females for fatty liver. Liver fibrosis/cirrhosis was seen more in females (n=6) than males (n=2).

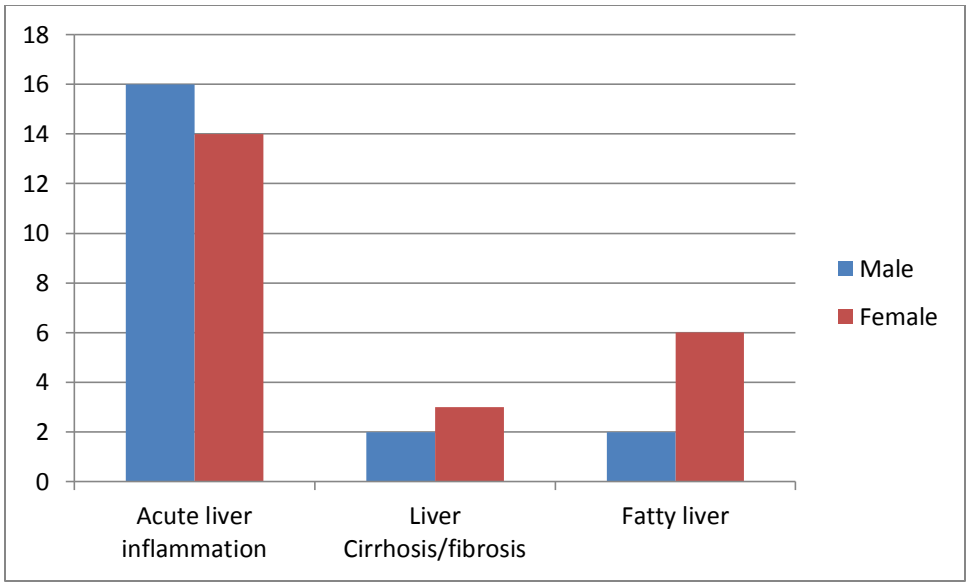


Figure 6: Bar chart showing distribution of hepatocellular jaundice as per gender

4.6 Distribution of Obstructive Jaundice as Per Age.

Most (50%) of the obstructive cases were from 50 years and above and were mainly pancreatic head masses, gall bladder masses and gall stones

Table 4: Distribution of obstructive jaundice as per age

Obstructive

	≤20	21-30	31-40	41-50	51-60	61-70	≥70
Pancreatic head mass	**0**	**0**	**2**	**1**	**0**	**2**	**4**
Gall stones	**0**	**1**	**1**	**1**	**0**	**1**	**2**
Cholecystitis	**1**	**2**	**1**	**2**	**1**	**0**	**2**
Gall bladder mass	**0**	**0**	**0**	**1**	**2**	**0**	**1**
Liver mass	**0**	**0**	**0**	**1**	**0**	**0**	**0**

4.7 Distribution of hepatocellular jaundice as per age:

Cases of acute inflammation of the liver were seen mostly in patients under 30 years: 22 cases out of a total of 30 (73%). Out of the 5 cases of fatty liver, 4 were in patients aged 40years and above. However, one case was in a patient under 30years.

Table 5: distribution of hepatocellular jaundice as per age

Hepatocellular Jaundice	≤20	21-30	31-40	41-50	51-60	61-70	≥70
Acute inflammatory	**9**	**13**	**4**	**2**	**1**	**1**	**0**
Fatty liver	**0**	**1**	**0**	**2**	**2**	**0**	**0**
Fibrosis	**0**	**2**	**2**	**2**	**2**	**0**	**0**

Table 6: Summary of Ultrasonographic Diagnoses

Variable	Overall n (%)	Obstructive n	Hepatocellular n	**Normal n**
Liver mass	79			
Yes	3 (4%)	1	2	0
No	76 (96%)	24	44	11
Acute liver inflammation	79			
Yes	30 (38%)	2	30	0
No	49 (62%)	23	16	11
Pancreatic head mass	79			
Yes	9 (11%)	9	0	0
No	70 (89%)	16	46	11
Liver fibrosis	79			
Yes	8 (10%)	0	8	0
No	71 (90%)	25	38	11
Gall bladder mass	79			
Yes	4 (5%)	4	1	0
No	75 (95%)	21	45	11
Gall stones	79			
Yes	6 (8%)	6	0	0
No	73 (92%)	19	46	11
Cholecystitis	79			
Yes	9 (11%)	9	0	0
No	70 (89%)	16	46	11
Fatty Liver	79			
Yes	5 (6%)	0	5	0
No	74 (94%)	25	41	11
Liver cyst	79			
Yes	1 (1%)	0	0	1
No	79 (99%)	25	46	11
Normal	**79**			
Yes	**11 (13%)**	**0**	**0**	11
No	**66 (84%)**	**25**	**46**	0

4.8 Ultrasound Features of Various Hepatobiliary Lesions

Features of different hepatobiliary lesions as found on ultrasound are captured below.

4.8.1 Hepatocellular lesions

Ultrasound Features of Acute Liver Inflammation (Acute Hepatitis)

The most common feature of acute liver inflammation was reduced parenchymal echogenicity which was present in 100% of the cases. Ninety percent of the cases had hepatomegaly while 10% had a normal sized liver. The classical "starry sky" appearance was seen in 86% of the cases.

Table 7: Ultrasound Features of Acute Liver Inflammation

Liver size	Normal	3 (10%)
	Enlarged	27 (90%)
	Hypoechoic	30 (100%)
Colour doppler	Normal	23 (76%)
	Increased	7 (24%)
Gall bladder findings (wall thickening, reduced or non-visualized GB)	Yes	21 (70%)
	No	9 (30%)
Starry sky liver	Yes	26 (86%)
	No	4 (14%)

Ultrasound features of Fatty liver

One hundred percent of patients with fatty liver had a diffuse pattern of fatty infiltration as well as hepatomegaly and increased parenchymal echogenicity. Focal fatty infiltration of the liver was not reported in this study. Preserved vascular demarcation was present in 45% of the cases while in 55% of case vascular demarcation was lost.

Table 8: Ultrasound features of Fatty liver

Liver size	Normal	0 (0%)
	Enlarged	5 (100%)
	Reduced	0 (0%)
Echotexure	Normal	0 (0%)
	hypoechoic	0 (0%)
	hyperechoic	5 (100%)
	heterogeneous	0 (0%)
Vascular demarcation	Present	2 (40%)
	Lost	3 (60%)
Pattern of fatty infiltraton	diffuse	5 (100%)
	focal	0 (0%)

Ultrasound Features of Liver Cirrhosis

Liver surface nodularity was the most common ultrasound feature of liver cirrhosis noted in 90% of the cases. Eighty seven percent of the cases had a shrunken liver with 13% showing normal sized liver. No case of hepatomegaly was seen. The most common parenchymal echopattern was the coarse heterogeneous type noted in 87% of the cases. A hyperechoic echopattern was seen in 13% of the cases. Ascites was an ancillary finding noted in 90% of the cases. The normal hepatopetal portal venous flow was seen in 60% of the cases while in 40% of the cases hepatofugal (reversed flow) was noted in the portal vein.

Table 9: Ultrasound Features of Liver Cirrhosis/Fibrosis

Liver size	Normal	13%
	Reduced	87%
	Enlarged	0%
Echotexure	Normal	0
	hypoechoic	0
	hyperechoic	13%
	Coarse, heterogeneous	87%
Presence of ascites	Yes	90%
	NO	10%
Surface nodularity	Yes	90%
	Non	10%
Portal venous flow	Hepatofugal	40%
	Hepatopetal	60%

4.8.2 Obstructive Lesions

Ultrasound Features of Pancreatic Mass

One hundred percent of the cases had a solitary mass located in the head of the pancreas. Most of the lesions (80%) were more than 2cm in its maximal dimension, with 20% measuring 2cm or less. The most predominant echopattern was the hypoechoic type at 60%. Colour doppler showed peripheral vascular encasement of the mass in 60% of the cases.

Table 10: Ultrasound features of pancreatic mass

Number	Solitary	100%
	Multiple	0
Tumor location	Pancreatic head	100%
	Other locations	0%
Mass size	>2cm	80%
	2cm or less	20%
Echotexure	Normal	0%
	hypoechoic	60%
	hyperechoic	0%
	heterogeneous	40%
Shape of mass	Ovoid/spherical	55%
	irregular	45%
Color doppler	Normal	30%
	increased	10%
	Reduced	0
	Peripheral vascular encasement	60%

Ultrasound features of gallstones

The most common features of gallstones were those of echogenic masses with posterior acoustic shadowing noted in all the cases. A non-visualized gallbladder with bright echoes filling the gallbladder fossa was noted in 67% of the cases. In 33% of the cases the gallstones were impacted in the gallbladder neck.

Table 11: Ultrasound Features of Gallstones

Location	Impacted in Gb neck	2 (33%)
	Non-visualized GB with bright echoes filling GB fossa	4 (67%)
Gravity dependence	Yes	0 (0%)
	No	6 (100%)
Echotexture	Hypoechoic	0 (0%)
	Hyperechoic	6 (100%)
Posterior shadowing	Yes	100%
	No	0 (0%)

Ultrasound features of gall bladder mass

A mass engulfing the gallbladder fossa with the lumen not visualized was the most common feature of gallbladder mass, noted in 75% of the cases. In 25% of the cases, the features were that of a mass arising from the gallbladder wall and protruding into the lumen with lumen intact. Diffuse gallbladder wall thickening as a feature of gallbladder masses was not reported in this study.

4.9 Laboratory Findings

The laboratory values are shown in **Table 12.** Generally, participants whose jaundice was categorized as hepatocellular based on ultrasonography had relatively higher levels of AST and ALT compared to those with obstructive jaundice. Those with ultrasonographic obstructive jaundice had higher levels of ALP, GGT and bilirubin compared with those with hepatocellular jaundice.

Table 12: summary of laboratory values

Variable	Median (IQR)			Reference values
	Overall	**Obstructive**	**Hepatocellular**	
ALT (U/L) *	134 (52-678)	66(39-77)	379 (79-1334)	0-41
AST (U/L) **	144 (81-658)	81(40-131)	319(144-1221)	0-38
ALP (U/L) ***	246 (120-482)	520(386-787)	179(120-285)	40-129
GGT (U/L) ******	170 (71-370)	203(160-708)	159(71-302)	10-66
Albumin (mg/dl)	35.7 (28-40)	35(31-38)	34(26-41)	35-50
Total bilirubin (umol/L)	223 (149-401)	401(175-461)	222(181-345)	0-17
Direct bilirubin (umol/L)	193 (113-394)	333(146-390)	191(124-225)	0.3-4

***ALT-Alanine transaminase**
****AST-Aspartate transaminase**
*****ALP-Alkaline Phosphatase**
******GGT-Gamma Glutamyl transferase**

The ratios between various liver enzymes as well as Direct/Total Bilirubin have been presented in **Table 13.** The median AST/ALT ratio was 1.07. Only 23% of the participants had an AST/ALT ratio >2. Ninety-five per cent of participants had a direct/total bilirubin ratio of >50%.

Table 13: Summary and interpretation of liver enzyme ratios

		Median (IQR); n (%)	
Variable	**Overall**	**Obstructive**	**Hepatocellular**
AST/ALT ratio*	1.07 (0.88-1.74)	1.16(0.92-1.28)	1.05(0.88-2.18)
ALT/ALP ratio (RValue)**	0.55(0.17-3.0)	0.15(0.05-0.25)	2.17(0.43-7.3)
Direct/total bilirubin (D/T) ratio (%) ***	81.6 (76.4-85.7)	83(81-85)	81(74-86)
AST/ALT ratio >2			
Yes	18 (23%)	2	13
No	61 (77%)		
DT Ratios proportions			
<20%	1(1.2%)	0	0
30-40%	1(1.2%)	0	0
>50%	75 (95%)	25	44
Other	2 (2.6%)	0	0
R value≥ 5 and D/T ≤ 0.5			
Yes	0	0	0
No	79	25	46
R value ≤ 2 and D/T ≥ 0.5			
Yes	50 (63%)	25	20
No	29 (37%)	0	26

*AST/ALT ratio: Ratios more than 2 are strongly suggestive of alcoholic liver disease
** ALT/ALP ratio (R-value)

- R VALUES ≥ 5 and D/T ≤ 0.5 are treated as positive diagnostic standar for hepatocellular jaundice.
- R VALUES ≤ 2 and D/T ≥ 0.5 are treated as positive diagnostic standard for cholestatic jaundice

***D/T ratio (%): <15- 20% hemolytic jaundice
30-40% hepatocellular jaundice, >50-60% cholestatic jaundice

4.10 Correlation between Liver enzymes/liver Enzyme Ratios with the Different Categories of Jaundice

Various liver enzymes and liver enzyme ratios were compared to determine whether they were associated with any particular category of jaundice as determined by ultrasound. Since the data were not normally distributed, these comparisons were done using the non-parametric Wilcoxon rank-sum test. The results are summarised in **Table 14.**

As illustrated, higher transaminase (AST and ALT) values were associated with hepatocellular jaundice whereas higher ALP, GGT and bilirubin (total and direct) values were associated with obstructive jaundice. However, it was noted that the direct/total bilirubin ratio was higher than expected in the hepatocellular group. There was a statistically significant difference in the median R-value between obstructive jaundice (R-value 0.15; 95% CI 0.05-0.25) and hepatocellular jaundice (R-value 2.17 95% CI 0.43-7.3); p 0.0001

Table 14: Correlation between Selected Liver Enzymes/Liver Enzyme Ratios with Ultrasonographic Category of Jaundice

Variable	**Ultrasonographic category of jaundice Median (IQR)**		**P value**
	Obstructive	**Hepatocellular**	
ALT (U/L) *	66(39-77)	379 (79-1334)	**0.0007**
AST (U/L) **	81(40-131)	319(144-1221)	**0.0001**
ALP (U/L) ***	520(386-787)	179(120-285)	**0.0001**
GGT (U/L) ****	203(160-708)	159(71-302)	**0.005**
Total bilirubin (umol/L)	401(175-461)	222(181-345)	**0.02**
Direct bilirubin (umol/L)	333(146-390)	191(124-225)	**0.002**
AST/ALT ratio*	1.16(0.92-1.28)	1.05(0.88-2.18)	0.92
ALT/ALP ratio (R Value)**	0.15(0.05-0.25)	2.17(0.43-7.3)	**0.0001**
Direct/total bilirubin (D/T) ratio (%) ***	83(81-85)	81(74-86)	**0.02**

SONOGRAPHIC IMAGES

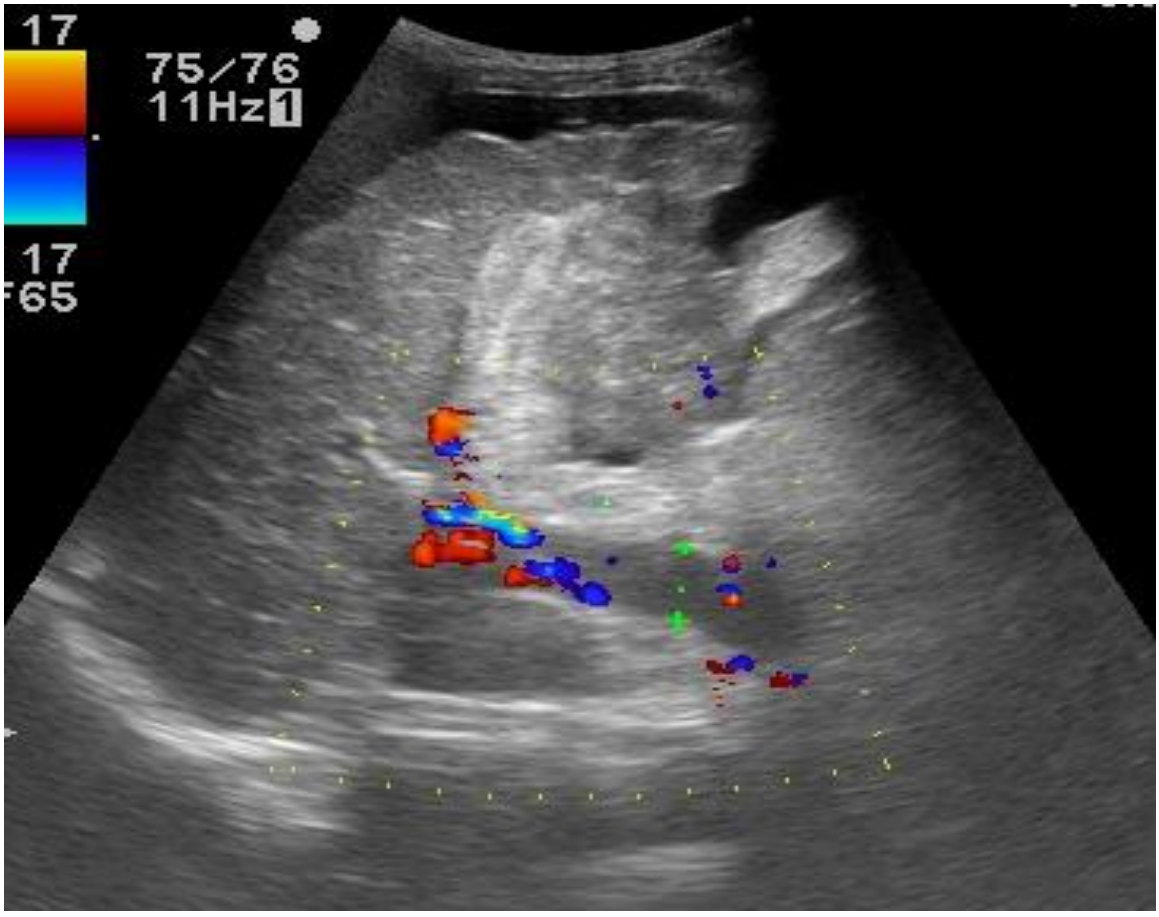


Figure 7: Case of a 53year old female with liver cirrhosis. The liver appeared shrunken with surface nodularity. Ascites was also noted.

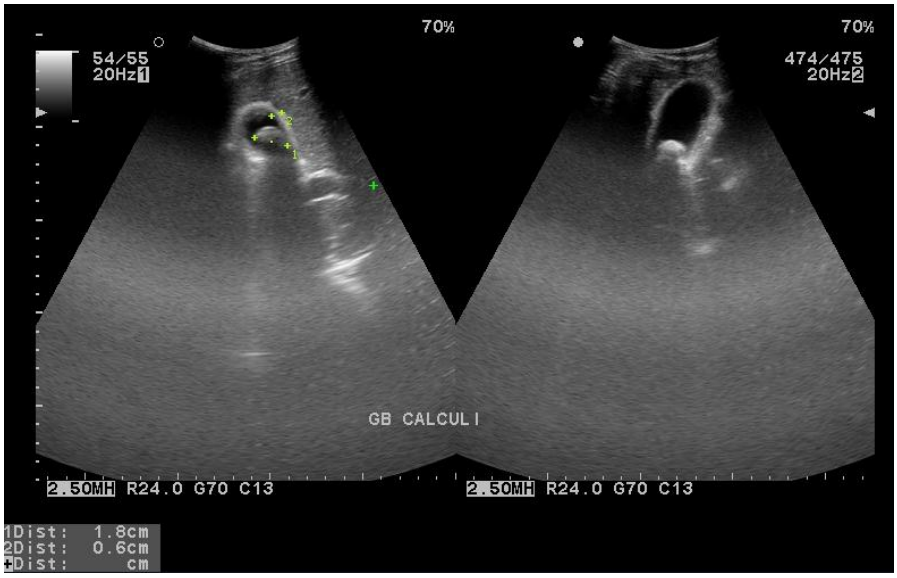


Figure 8: Case of a 37yo female with GB calculi. An echogenic mass with posterior acoustic shadowing was noted in the GB neck.

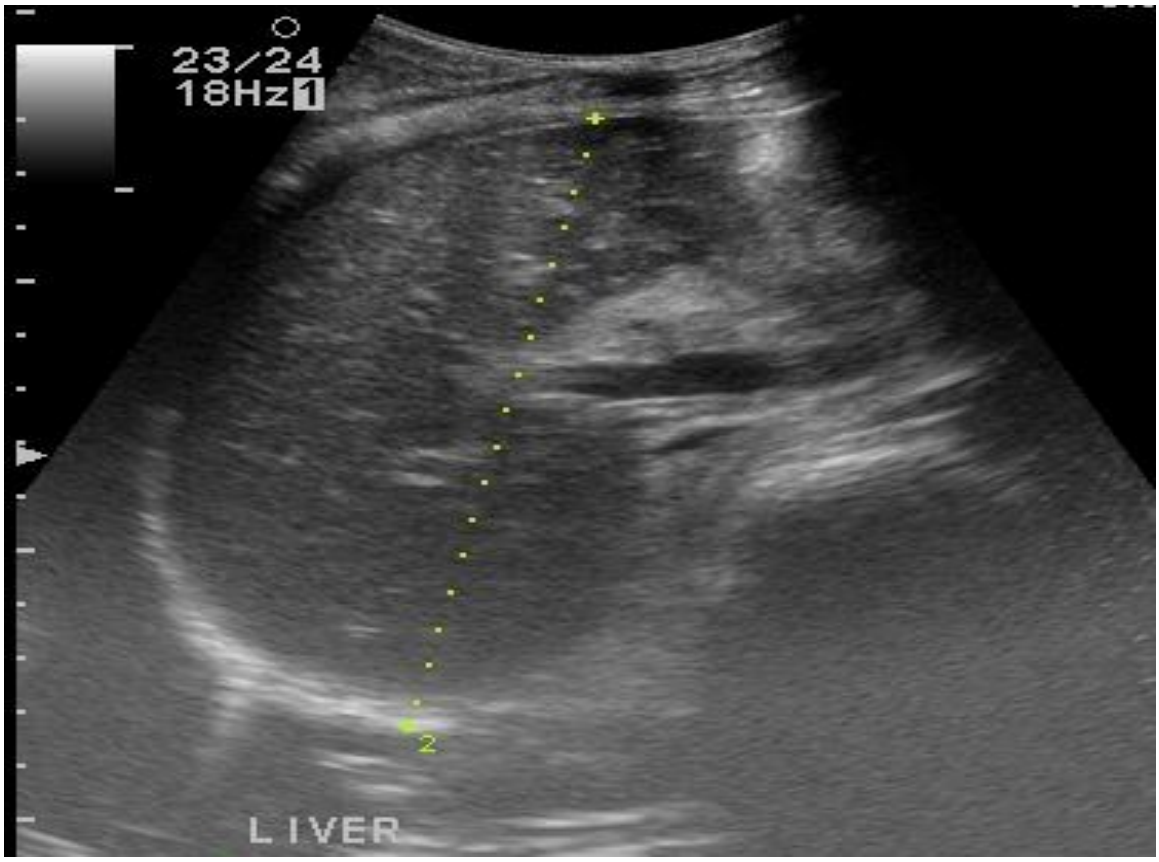


Figure 9: A case of a 20yo university student with acute inflammation of the liver (hepatitis). There was accentuation of the portal vein radicals against a hypoechoic background of the inflamed liver parenchyma giving it a 'starry sky' appearance.

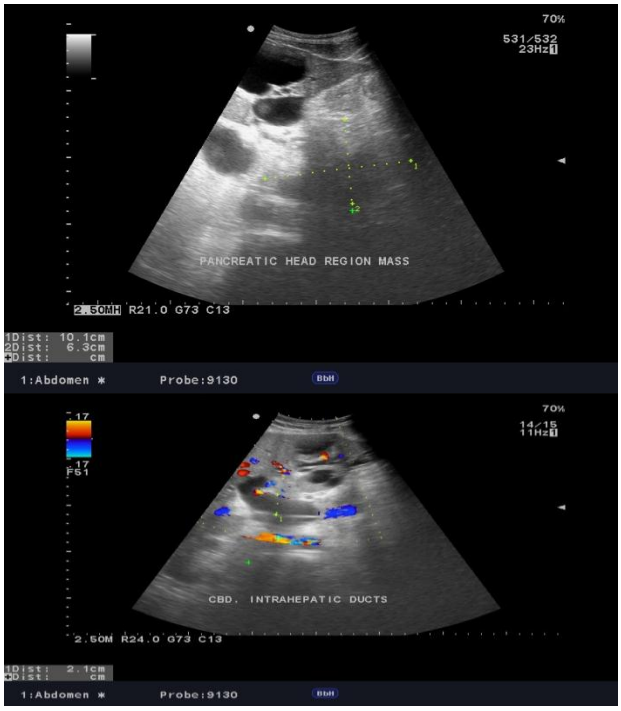


Figure 10: Case of a 58year old female with pancreatic head mass causing CBD obstruction with dilatation of intra and extrahepatic bile ducts

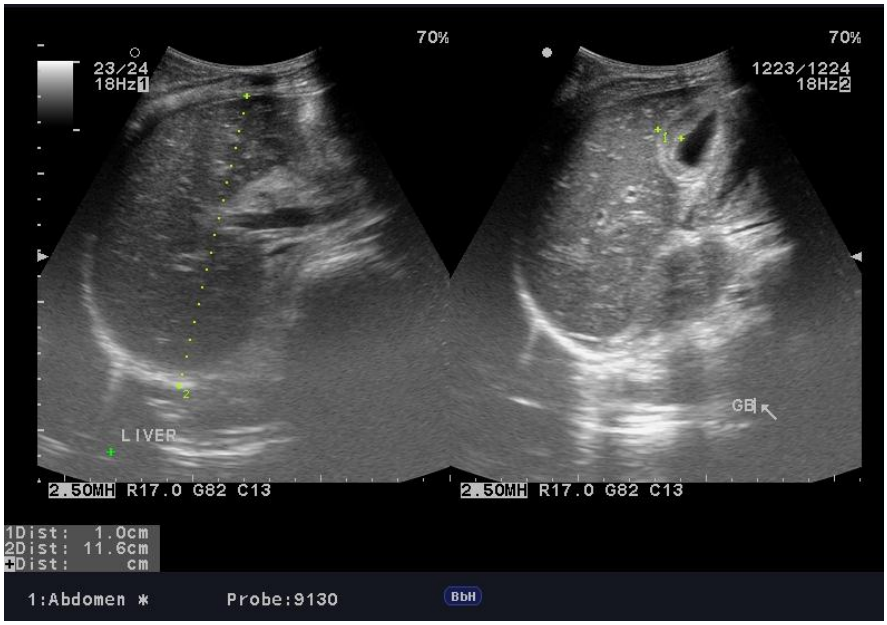


Figure 11: Case of acute hepatitis with associated gallbladder findings. The liver had a starry sky appearance with the gall bladder wall appearing thickened.

CHAPTER FIVE: DISCUSSION

5.1 Demographics of Participants

In this study 79 participants were recruited, majority of whom were females, constituting 52%.

5.2 Ultrasound Findings

Overall, the main cause of jaundice as determined by ultrasound was attributed to acute inflammation of the liver (acute hepatitis) (38%) followed by pancreatic head mass (11%) and liver fibrosis (10%). These findings were similar to those at KNH where Hepatitis was the commonest finding followed by pancreatic head cancer (Githuku 2009). This differed with a study in South Wales where Malignancies were found to be the commonest causes of jaundice (34%), with hepatitis coming in at a distant 5^{th} with 3% (Whitehead, Hainsworth et al. 2001). This could be explained by the socio-economic factors where infective viral conditions are more common in lower income countries like Kenya compared to Western countries.

Fifty-six per cent of the participants had hepatocellular type of jaundice whereas 31% had obstructive type. The remaining 13% had normal sonographic findings. This relates well with a study by Githuku at KNH where 57% of the participants had hepatocellular jaundice and 43% had obstructive type of jaundice (Githuku 2009). It however differs with a study in China which found majority of the patients (55%) to have obstructive type of jaundice (Yu, Fu et al. 2012). The difference could be explained by the fact that China and other Western countries report less cases of infective forms of hepatitis which make the bulk of the hepatocellular form of jaundice in Kenya and Africa at large.

Pancreatic head mass made majority of the obstructive category of jaundices, findings that were similar to Githuku's study at KNH, where pancreatic head cancer made 60% of the cases of obstructive jaundice (Githuku 2009). These findings were also similar to those found by Ngoseywe at KNH where 57% of the participants had cancer of the head of the pancreas (Ngoseywe 2008).

Thirteen per cent of the participants had normal hepatobiliary ultrasound findings despite having clinical and laboratory evidence of jaundice. Morphologic changes are thought to lag behind biochemical and immunological changes in cases of acute hepatitis. Githuku demonstrated this in the KNH study where he found that 34% of participants with positive immunoassays for hepatitis viruses did not have any hepatobiliary ultrasound abnormalities (Githuku 2009).

Majority of the patients with hepatocellular type of jaundice were noted to be under 30years of age especially in acute inflammatory conditions. This study found majority of the patients with acute liver inflammation (hepatitis) to be students from surrounding colleges. This could be attributed to enteric forms of hepatitis viral infections which have been shown to be a major cause of acute viral infection in the developing world (Labrique, Thomas et al. 1999). These infections have been reported to occur in outbreaks through contaminated water and tend to affect learning institutions.

In this study, there were more males than women with pancreatic head mass though the sample size (9) was too small to derive a statistically significant conclusion. Most of these patients with pancreatic head mass (6 out of 9) were aged 60years and above. This is the case with most malignancies.

6 patients had gall stones, with females being the majority (4 out of 6). Notable was that one patient was under 30years of age. This could be explained by lifestyle change. A study at KNH (Githuku 2009) and another in Germany (Kratzer, Kachele et al. 1998) also noted this trend where gallstones are being reported in a much younger population.

5.3 Ultrasound features of Different Hepatobiliary Lesions.

5.3.1 Ultrasound Features of Acute Inflammatory Liver Conditions

All patients with acute inflammatory conditions of the liver had reduced liver echogenicity. Ninety per cent were noted to have hepatomegaly. Reduced liver echogenicity and hepatomegaly are a well-established criteria for diagnosis of acute inflammatory conditions of the liver on ultrasound (Tchelepi, Ralls et al. 2002).

Gall bladder findings were a common occurrence in acute inflammatory conditions of the liver (70%). The most recurring findings were a collapsed or non-visualized gall bladder with increased mural thickness and pericholecystic fluid. These findings are consistent with findings from previous studies (Sharma and Dasarathy 1991, Sudhamsu 2006, Githuku 2009, Suk, Kim et al. 2009). Several hypotheses have been proposed to explain the mechanism of gallbladder wall thickening in these patients. One hypothesis is that gallbladder wall thickening, together with a decrease in gallbladder volume, occurs when injury to the hepatocytes at the time of onset of acute hepatitis causes a temporary decrease in bile production and excretion (Sharma and Dasarathy 1991). Another hypothesis proposes that mural thickening of the gallbladder is due to a direct injury to and inflammation of the mucosal and muscular layers of the gallbladder by hepatitis virus contained in bile juice (Dogra, Singh et al. 1995). This hypothesis is based on reports

showing that hepatitis virus was detected in the bile juice of infected monkeys and that hepatitis A virus antigen was detected in the gallbladder and bile duct of patients diagnosed with hepatitis A and related acalculous cholecystitis (Mourani, Dobbs et al. 1994). A third hypothesis is that hepatocyte necrosis, which is extensive in patients with acute hepatitis, causes an inflammatory reaction in the tissues surrounding the liver, including the gallbladder wall (Jüttner, Ralls et al. 1982) . Thus, ultrasonographic findings of the gallbladder are present in most of the acute viral hepatitis. Literature suggests that these findings can be used as ancillary findings in case of acute viral hepatitis. When serological diagnostic facilities are not available it can back up the diagnosis when clinically acute hepatitis is suspected. These findings of gallbladder have recently been verified by more accurate technique of endoscopic ultrasonography (Kim, Baik et al. 2003).

A starry sky liver was seen in 86% of cases of acute hepatitis. This was in contrast with a study at KNH that showed only 16% of patients with acute hepatitis to have the classical starry sky pattern. It also contradicts another study that found only 19 of the 791 patients studied to have viral hepatitis (Giorgio, Amoroso et al. 1986).

5.3.2 Ultrasound Features of Liver Cirrhosis

In our study, liver surface nodularity was seen in 90% of patients with liver cirrhosis. Similarly, surface nodularity was seen in 88% of patients with confirmed cirrhosis in a study by Di Lelio (Di Lelio, Cestari et al. 1989). 91% of participants were found to have surface nodularity in a study by Simonovsky (Simonovský 1999). Liver surface nodularity in patients with cirrhosis is thought to be due to alternating areas of necrosis and regenerative nodules. Necrosis results in varying degrees of fibrosis with collapse of

the underlying liver parenchyma and capsular retraction, while regenerating nodules cause random areas of contour bulging. In macronodular disease, the characteristic surface nodularity is typically present. However, with micronodular disease, the hepatic surface may be smooth or nodular (Kreuer S 2016).

Eighty-seven per cent of patients with liver cirrhosis had reduced liver sizes. There was also ascites as an ancillary finding pointing towards chronicity. These findings were also noted by Githuku at KNH (Githuku 2009).

40% of patients with liver cirrhosis had the normal hepato-petal portal venous flow on doppler, much higher than what Gaiani et al found (8%) (Gaiani, Bolondi et al. 1991). This could be explained by the fact that Giaini studied a non-selected population of patients with liver cirrhosis whereas in this study, only patients with liver cirrhosis who presented with jaundice were studied. Our group therefore had patients with more advanced cirrhosis with reversed porto-venous flow.

5.3.3 Ultrasound Features of Pancreatic Mass

All the pancreatic masses were located within the pancreatic head and were solitary masses measuring more than 2cm in diameter. They were predominantly hypoechoic to heterogeneously hypoechoic. Peripheral vascular encasement was seen in 60% of the cases. In 55% of the cases, the masses were ovoid/spherical while in 45% of the cases,the masses were irregular. These findings compared well with what Yassa et al. found. Yassa found 80% of the masses to measure 4.5x 3.5cm on average, 55% to be hypoechoic, 45% heterogeneous, 60% ovoid/spherical. He also found peripheral vascular encasement in

45% of cases (Yassa, Yang et al. 1997). He however found only 69% of the tumors to be in the pancreatic head. The difference in location could be explained by the fact that Yassa studied all pancreatic masses unlike in this study where only those masses causing jaundice were evaluated.

5.3.4 Ultrasound Features of Gall Bladder Mass

Two sonographic patterns were seen depending on whether the lumen of the gallbladder was visualized or not. In one patient (25%), the gallbladder lumen was demonstrated and an irregular fixed polypoid soft tissue mass with no posterior acoustic shadowing was seen arising from the gall bladder wall and projecting into the lumen. In the other three patients, a solid mass was seen in the predicted location of the gallbladder without visualization of gallbladder lumen. The mass was seen to infiltrate into the surrounding liver. These features were different from those found by Bangalore et al who demonstrated an intact gall bladder lumen in more patients (40%). It also contradicted a study by Weiner et al. (Weiner, Koenigsberg et al. 1984). This could be explained by the fact that the current study focused on patients who had presented with jaundice meaning the disease had quite progressed. These findings were similar to the KNH study (Githuku 2009).

Rooholamini et al reviewed 59 cases of histologically proven carcinoma of the gall bladder and found the following: Radiologic findings included focal or diffuse thickening of the gallbladder wall (49%), a mass in the gallbladder fossa (37%), and an intraluminal mass (14%). Associated findings were cholelithiasis (64%), biliary duct dilatation (38%), invasion of the adjacent structures (67%), distant metastases other than those of the liver (3%), and porcelain gallbladder (4%). (Rooholamini, Tehrani et al. 1994)

In another study: A descriptive and retrospective study was made of clinical features and imaging studies in patients subjected to surgery for gallbladder neoplasm in the Reina Sofía General University Hospital (Murcia) during the time period 2000–2011. Results: A total of 15 cases of gallbladder cancer were found during the study period. The ultrasound findings showed gallbladder wall thickening (>4 mm) in 8 cases, intraluminal mass in 4, scleroatrophic gallbladder in 2, and mass replacing the gallbladder in one (Maldonado, Lopez et al. 2014).

5.3.5 Ultrasound Features of Fatty Liver

All the cases of fatty liver (hepatic steatosis) were diffuse in nature and had features of increased echogenicity, blurring of portal vein radicles as well as non-visualization of the diaphragm consistent with grade 3 hepatic steatosis. This is because jaundice in fatty infiltration only occurs at an advanced stage where there is considerable infiltration and replacement of the hepatocytes with fat. Focal hepatic infiltration does not significantly impair liver function.

5.3.6 Ultrasound Features of Liver Masses

The 3 liver masses reported in this study showed one pattern; diffuse hepatic infiltration with poorly demarcated margins. No focal liver masses were seen.

5.3.7 Ultrasound Features of Gallstones

Six cases of gallstones were reported, and the features were those of echogenic masses with posterior acoustic shadowing. Four cases had gallstones impacted in the GB neck, while 2 cases had a non-visualized gallbladder with large collection of bright echoes with posterior acoustic shadowing (GB packed with stones) filling the gallbladder fossa.

5.4 Laboratory Findings

Generally, participants whose jaundice was categorized as hepatocellular based on ultrasonography had relatively higher levels of AST and ALT compared to those with obstructive jaundice. Those with ultra-sonographic obstructive jaundice had higher levels of ALP, GGT and bilirubin compared with those with hepatocellular jaundice. These findings were in keeping with the existing knowledge (Giannini, Testa et al. 2005, Kim, Flamm et al. 2008)

An estimated 95% of participants had a direct/total bilirubin ratio of >50%, contrary to the expectation that only obstructive conditions should have a ratio more than 50%. This was because many of the acute inflammatory conditions in this study may have been complicated by an element of cholestasis hence giving an obstructive picture. Studies abound of acute hepatitis complicated by cholestasis (Gordon, REDDY et al. 1984, Rizzetto 1999)

5.4.1 Correlation between Ultrasound Findings and Liver Enzymes and Liver Enzyme Ratios

There was a statistically significant difference in the median R-value between obstructive jaundice (R-value 0.15; 95% CI 0.055-0.25) and hepatocellular jaundice (R-value 2.17 95% CI 0.43-7.3); p 0.0001. This related well with a study in China that found that there was a statistically significant difference of R-values between obstructive jaundice and hepatocellular jaundice (Yu, Fu et al. 2012). There was also a statistically significant difference between the D/T ratios for obstructive jaundice (83%) and hepatocellular jaundice 81% with a p-value of 0.02. The Chinese study had found the D/T values for

cholestatic jaundice at 93% and hepatocellular jaundice at 16%, a much wider range than this study found. This could be explained by the fact that most of the acute forms of viral hepatitis (which form the bulk of hepatocellular jaundice in developing countries) are complicated by an element of cholestasis, giving an obstructive biochemical picture, hence the high D/T values for hepatocellular jaundice recorded in this study. Case reports have been documented of prolonged intrahepatic cholestasis secondary to acute viral hepatitis (Gordon, REDDY et al. 1984)

Traditionally, D/T ratio has been used in differentiating hepatocellular jaundice from cholestatic jaundice in combination with AST, ALT, ALP and GGT. However, overlaps in the D/T ratio as well as serum enzyme changes have been reported in cholestatic and hepatocellular jaundice. This has rendered the traditional approach unreliable in terms of sensitivity and specificity in the differential diagnosis of jaundice.

In the genotyping of drug induced liver disease, R-value has been widely used in clinical practice and has played an important role in guiding treatment of these patients.

The R value was established by the Council for International Organizations of Medical Sciences (CIOMS), and is the diagnostic criteria for dividing drug-induced liver diseases into hepatocellular, cholestatic or mixed type. This categorization is based on the R value which is the ratio between ALT and ALP.

ALT is a nonspecific intracellular enzyme found mainly in the liver. It is found in smaller quantities in the skeletal muscle, kidney, and cardiac tissues. Under normal circumstances, its serum levels are low, ranging from 10 to 40U/L. When the cells are damaged, the liver cell membrane permeability increases and the intracellular ALT is

released into the blood hence increasing the serum ALT levels. Studies have shown a relationship between ALT levels and age, gender and BMI (Andrade, Lucena et al. 2006, Grossi, Colombo et al. 2006). Chen demonstrated that the most common cause of ALT increase is non-alcoholic fatty liver (Chen, Huang et al. 2007).

On the other hand, ALP is a nonspecific enzyme which catalyzes the hydrolysis of organic single phosphate. ALP is found mainly in the liver and bone, with the metabolism of this enzyme varying depending on the tissue of origin. In biliary obstruction, liver masses or infiltrative liver lesions, serum ALP rise is seen ahead of bilirubin rise, and in some cases ALP rise can be seen without increase in bilirubin levels. Serum ALP has traditionally been measured in the differential diagnosis of liver lesions and obstructive jaundice, and it is of greater reference value when measured together with transaminases (ALT and AST). This has shown that serum ALP determination has diagnostic significance with high sensitivity for hepatobiliary disease.

In this study, it was demonstrated that there was a significant difference in the R values between hepatocellular type of jaundice and cholestatic type of jaundice as seen on ultrasound.

For hepatocelluar jaundice, the R-value is more sensitive. This may be because in the initial stages of liver cell injury, the ability of damaged cells to take up bilirubin for conjugation and excretion is impaired, but undamaged liver cells can still partly compensate for their functions of converting unconjugated bilirubin into conjugated bilirubin which is excreted from the biliary tree. When the rate of formation of conjugated bilirubin exceeds its excretion, its blood levels increase, so in the initial stages

of hepatocyte damage the increase may not be so pronounced. While due to membrane permeability decreases for the damaged liver cells, the intracellular ALT is released into the blood in large proportions and ALT increases several times.

On the other hand, the swollen hepatocytes exert oppressive effect on the bile ducts causing only mild elevation in ALP. So, the R value increases significantly during hepatocyte damage and this happens earlier than bilirubin increase.

CHAPTER SIX: CONCLUSIONS AND RECOMMENDATIONS

6.1 Conclusions

Acute inflammatory conditions of the liver with a hypoechoic liver and a starry sky appearance were the commonest findings among the hepatocellular type, with pancreatic head masses being the commonest among the obstructive type of jaundice as seen on ultrasound. There was a statistically significant difference between the alanine transaminase (ALT): alkaline phosphatase (ALP) ratio (R-value) for obstructive and hepatocellular jaundice as seen on ultrasound.

6.2 Recommendations

There should be a high index of suspicion for acute inflammatory conditions of the liver and pancreatic head masses when scanning younger and elderly patients with jaundice respectively. A larger study to check for true associations between the ALT: ALP ratio (R-value) and hepatocellular and obstructive types of jaundice.

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APPENDICES

Appendix I: Consent Form

English Version

Investigator: My name is Dr. MASONI Isaac. I am a qualified doctor, registered with the Kenya Medical Practitioners and Dentists Board. I am currently pursuing a Masters degree in Radiology and Imaging at Moi University. I would like to recruit you into my research which is to study the Ultrasound findings in patients with jaundice at Moi Teaching and Referral Hospital.

Purpose: This study will seek to determine the sonographic findings among patients presenting with jaundice.

Procedure: All patients jaundice referred for ultrasound scanning and for whom consent has been given will undergo US evaluation. Demographic data will be obtained and the patients subjected to a physical examination. Both the clinical and radiologic data will be collected on data collection forms. Data collecting material will be kept in a locked cabinet during the study period.

Benefits: There will be no direct benefits of participating in this study. Study subjects will be accorded same quality of management as non-study subjects

Risks: There are no anticipated risks to the participants attributable to this study.

Confidentiality: All information obtained in this study will be treated with utmost confidentiality and shall not be divulged to any unauthorized person

Rights to Refuse: Participation in this study is voluntary, there is freedom to refuse to take part or withdraw at any time. This study has been approved by the Institutional Research and Ethics Committee (IREC) of Moi University/Moi Teaching and Referral Hospital.

Sign or make a mark if you agree to take part in the study

Parent/Guardian: …… Investigator: …….Date: ……

Kiswahili Version

Mtafiti: jina langu ni Dkt. MASONI Isaac. Mimi nidaktarialiyehitimu na kusajiliwa na bodi ya Kenya ya Madaktari na Madaktari wa meno. Kwa sasa natafuta shahada ya uzamili katika Radiology na Imaging katika Chuo Kikuu cha Moi. Ningependa kukusajili katika utafiti wangu ambao ni wa kuangalia baadhi ya magonjwa ambayo yanasababisha macho na sehemu zingine za mwili kaubadili rangi na kuwa manjano kwa kutumia picha ya Ultrasound.

Kusudi: Utafiti huu utajaribu kueleza namna mbalimbali ya magonjwa ya ini, na yanayosababisha macho na viungo vingine vya mwil kuwa manjano, yataonekana kwenye picha ya Ultrasound.

Utaratibu: Wagonjwa wote ambao wana rangi ya njano kwenye macho , watashirikishwa kwenye utafiti huu ikiwa watakubali. Data zitakusanywa kwenye fomu za ukusanyaji data. Hifadhi zitakazotumika katika ukusanyaji wa data zitawekwa katika kabati iliyofungwa katika chumba cha mpelelezi mkuu kwa kipindi cha utafiti.

Faida: Hakutakuwa na faida moja kwa moja ya kushiriki katika utafiti huu.Wanaofanyiwa utafiti watakuwa na haki ya kupewa matibabu sawa na wale ambao hawatahusishwa kwenye utafiti huu.

Hatari: Hakuna hatari ya kutarajia kwa washiriki kutokana na utafiti huu.

Usiri: habari zote zitakazopatikana katika utafiti huu wa kutibiwa zitawekwa kwa usiri mkubwa na wala haitatolewa kwa mtu yeyote asiye husika na utafiti.

Haki ya kukataa: Kushiriki katika utafiti huu ni hiari yako, kuna uhuru wa kukataa kushiriki au kujiondoa wakati wowote. Utafiti huu umepitishwa na Utafiti wa Taasisi na Kamati ya Maadili (IREC) ya Chuo Kikuu cha Moi na Hospitali ya Rufaa.

Weka sahihi au alama kama umekubali kushiriki katika utafiti

Mzazi / Mlezi: ..... Mtafiti: .....

Tarehe: .....

Appendix II: Data Collection Form

SOCIO-DEMOGRAPHICS

Date: ……. Medical Record Number: ……

Serial Number…….

Age……

Gender……Male ☐ Female ☐

County of residence.....

Level of education None ☐ Primary ☐ secondary ☐ Tertiary ☐

Alcohol use Yes ☐ No ☐

History of viral Hepatitis A ☐ B ☐ C ☐ None ☐

History of non-viral hepatitis Chemical ☐ fungal ☐

CLINICAL FINDINGS

Any history of yellow eyes…….

Duration of jaundice……..

History of Dark urine……Yellow urine……..

Pale stools……

Pruritus……..

Physical examination

Yellow eyes yes ☐ No ☐

Liver span: Average ☐ increased ☐ Reduced ☐

Laboratory tests

ALT: Normal ☐ Increased (No. of times the ULN) ☐

AST Normal ☐ Increased (No. of times the ULN) ☐

ALP: Normal ☐ Increased (No. of times the ULN) ☐

GGT: Normal ☐ Increased (No. of times the ULN) ☐

AST/ALT Ratio:

ALT/ALP Ratio (R Value):

Albumin Levels: Normal ☐ Increased ☐ Reduced ☐

Total(T) bilirubin levels: Normal ☐ Increased ☐ Reduced ☐

Direct(D) Bilirubin levels……

Indirect bilirubin levels……

Direct/ Total bilirubin (D/T) Ratio……

ULTRASOUND EXAMINATION

Liver Size Normal ☐ Reduced ☐ Enlarged ☐

Echogenicity Average ☐ Hypoechoic ☐ Hyperechoic ☐ Heterogenous ☐

Colour flow: Hepatic artery Normal ☐ Reduced ☐ Absent ☐

Main portal vein Normal ☐ Reduced ☐ Absent ☐

Presence of mass/masses……Yes ☐ No ☐

Solid ☐ Cystic ☐ Mixed ☐

Solid Masses Solitary ☐ Multiple ☐

Hypoechoic ☐ Isoechoic ☐ Hyperechoic ☐ Heterogenous ☐

Size (measurements) Small ☐ Medium ☐ Large ☐

Vascularity Normal ☐ reduced ☐ Increased ☐

Location of mass Right lobe ☐ Left lobe ☐

Cystic masses Solitary ☐ Multiple ☐

Hypoechoic ☐ Isoechoic ☐ Hyperechoic ☐ Heterogenous ☐

Size Small ☐ Medium ☐ Large ☐

Location of mass Right lobe ☐ Left lobe ☐

Portal vein

Diameter (measurements) Normal ☐ Increased ☐ Decreased ☐

Doppler Flow to the liver Centripetal ☐ Centrifugal ☐

Velocity Normal ☐ Increased ☐ Decreased ☐ Reversed ☐

Capsule Smooth ☐ Irregular ☐ nodular ☐ Thickened ☐

Bile ducts Average ☐ Dilated ☐ Not seen ☐

If dilated: Intrahepatic Right ☐ left ☐ Both ☐ common hepatic ☐

Exrahepatic CBD (diameter) ☐ Cystic duct (diameter) ☐

All dilated (intrahepatic and extrahepatic) ☐

Hepatic veins Normal ☐ Compressed ☐ dilated ☐ Others ☐

Any other findings…..

Gall bladder

Present ☐ **Absent** ☐

Size Normal ☐ Reduced ☐ Enlarged ☐

Wall thickness (in mms) ☐

Presence of mass: Mural ☐ Luminal ☐

Presence of stone yes ☐ No ☐

Presence of sludge Yes ☐ No ☐

Pancreas

Parenchymal echogenicity

Normal ☐ hypoechoic ☐ hyperechoic ☐ heterogenous ☐

Pancreatic head size Normal ☐ Reduced ☐ Enlarged ☐

Body Normal ☐ Enlarged ☐

Tail Normal ☐ Enlarged ☐

Pancreatic mass present ☐ absent ☐

Location……..Head ☐ Body ☐ Tail ☐

Size……. small ☐ Medium ☐ Large ☐

Nature: Solid ☐ Cystic ☐

Echogenicity

Hypoechoic ☐ Isoechoic ☐ hyperechoic ☐ Heterogenous ☐

Vascularity……..Average ☐ reduced ☐ Increased ☐

Causing biliary obstruction…… Yes ☐ No ☐

If yes……CBD ☐ Both CBD and Pancreatic duct ☐

Pancreatic duct Normal ☐ Dilated ☐

Calcifications……. Parenchymal ☐ Ductal ☐

Surrounding edema……Yes ☐ No ☐

Others…….. Yes No

Shrunken pancreatic parenchyma Yes ☐ No ☐

Other findings…….(e.g ampullary, duodenal, ampullary, stricture)

ULTRASOUND FINAL DIAGNOSIS

Liver mass (cholestatic) ☐

Acute Inflammatory liver disease (hepatocellular) ☐

Pancreatic head mass (cholestatic) ☐

Liver cirrhosis/fibrosis (Hepatocellular) ☐

Gall bladder mass (Cholestatic) ☐

Gall stones (Cholestatic) ☐

Fatty liver change (Hepatocellular) ☐

CBD stricture (Cholestatic) ☐

Pancreatitis (Cholestatic) ☐

Cholangiocarcinoma (Cholestatic) ☐

Liver cysts (Cholestatic) ☐

Other ☐

CATEGORY OF JAUNDICE

Cholestatic jaundice ☐

Hepatocellular jaundice ☐

Others ☐

Appendix III: Approval Letters

INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE (IREC)

MOI TEACHING AND REFERRAL HOSPITAL
P.O. BOX 3
ELDORET
Tel: 33471//2/3

MOI UNIVERSITY
SCHOOL OF MEDICINE
P.O. BOX 4606
ELDORET

Reference: IREC/2015/142
Approval Number: 0001471

26th August, 2015

Dr. Makokha Masoni,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

INSTITUTIONAL RESEARCH & ETHICS COMMITTEE
26 AUG 2015
APPROVED
P. O. Box 4606-30100 ELDORET

Dear Dr. Makokha,

RE: FORMAL APPROVAL

The Institutional Research and Ethics Committee has reviewed your research proposal titled:-

"Correlation of Ultrasound and Laboratory Findings in Adult Patients Presenting with Jaundice at Moi Teaching and Referral Hospital – Eldoret, Kenya".

Your proposal has been granted a Formal Approval Number: ***FAN: IREC 1471*** on 26th August, 2015. You are therefore permitted to begin your investigations.

Note that this approval is for 1 year; it will thus expire on 25th August, 2016. If it is necessary to continue with this research beyond the expiry date, a request for continuation should be made in writing to IREC Secretariat two months prior to the expiry date.

You are required to submit progress report(s) regularly as dictated by your proposal. Furthermore, you must notify the Committee of any proposal change (s) or amendment (s), serious or unexpected outcomes related to the conduct of the study, or study termination for any reason. The Committee expects to receive a final report at the end of the study.

Sincerely,

PROF. E. WERE
CHAIRMAN
INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE

cc Director - MTRH Dean - SOP Dean - SOM
Principal - CHS Dean - SON Dean - SOD

INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE (IREC)

MOI TEACHING AND REFERRAL HOSPITAL
P.O. BOX 3
ELDORET
Tel: 33471//2/3

MOI UNIVERSITY
SCHOOL OF MEDICINE
P.O. BOX 4606
ELDORET
Tel: 33471/2/3

Reference IREC/2015/142
Approval Number: 0001471

5th June, 2017

Dr. Makokha Masoni,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

INSTITUTIONAL RESEARCH & ETHICS COMMITTEE
05 JUN 2017
APPROVED
P. O. Box 4606-30100 ELDORET

Dear Dr. Makokha,

RE: APPROVAL OF AMENDMENT

The Institutional Research and Ethics Committee has reviewed the amendment made to your proposal titled:-

"Correlation of Hepatobiliary Ultrasound Findings with Liver Enzymes in Adult Patients with Jaundice at Moi Teaching and Referral Hospital, Eldoret- Kenya".

We note that you are seeking to make an amendment as follows:-

1. To change the title to above from ***"Correlation of ultrasound and laboratory findings in adult patients presenting with jaundice at Moi Teaching and Referral Hospital, Eldoret, Kenya".***

The amendment has been approved on 5th June, 2017 according to SOP's of IREC. You are therefore permitted to continue with your research.

You are required to submit progress(s) regularly as dictated by your proposal. Furthermore, you must notify the Committee of any proposal change(s) or amendment(s), serious or unexpected outcomes related to the conduct of the study, or study termination for any reason. The Committee expects to receive a final report at the end of the study.

Sincerely,

PROF. E. WERE
CHAIRMAN
INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE

cc: CEO - MTRH Dean - SPH Dean - SOM
Principal - CHS Dean - SOD Dean - SON

Appendix IV: Hospital Approval

MOI TEACHING AND REFERRAL HOSPITAL

Telephone: 2033471/2/3/4
Fax: 61749
Email: director@mtrh.or.ke
Ref: ELD/MTRH/R.6/VOL.II/2008

P. O. Box 3
ELDORET

26th August, 2015

Dr. Makokha Masoni,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

RE: APPROVAL TO CONDUCT RESEARCH AT MTRH

Upon obtaining approval from the Institutional Research and Ethics Committee (IREC) to conduct your research proposal titled:-

"Correlation of Ultrasound and Laboratory Findings in Adult Patients Presenting with Jaundice at Moi Teaching and Referral Hospital – Eldoret, Kenya".

You are hereby permitted to commence your investigation at Moi Teaching and Referral Hospital.

DR. JOHN KIBOSIA
DIRECTOR
MOI TEACHING AND REFERRAL HOSPITAL

CC - Deputy Director (CS)
- Chief Nurse
- HOD, HRISM