DOPPLER ULTRASOUND FINDINGS AND FEATURES ASSOCIATED WITH PORTAL HYPERTENSION IN ADULTS PATIENTS WITH CLINICALLY DIAGNOSED LIVER CIRRHOSIS AT MOI TEACHING AND REFERRAL HOSPITAL, ELDORET, KENYA.

BY

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DECLARATION

I declare that this dissertation 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 and/or Moi University.

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DEDICATION

I would like to dedicate this work to the Almighty God for the gift of life. To my husband Dr. Dennis Muli, my sons Maverick and Marcel for their undying support. To my parents who continue to motivate me and fully support my career. To my siblings whose tremendous encouragement has motivated me to keep at it.

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LIST OF ABBREVIATIONS

ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CDC	Centre for Disease Prevention and Control
CI	Congestive Index
CSPH	Clinically Significant Portal Hypertension
DALYs	Disability Adjusted Life Years
HARI	Hepatic Artery Resistive Index
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HVPG	Hepatic Venous Pressure Gradient
IHVR	Intrahepatic Vascular Resistance
INR	International Normalized Ratio
IQR	Interquartile Range
IREC	Institutional Research and Ethics Committee
KMTC	Kenya Medical Training College
MHz	Megahertz
MRI	Magnetic Resonance Imaging
MTRH	Moi Teaching and Referral Hospital
NCHS	National Center for Health Statistics
NFPF	Non-forward Portal Flow
PI	Pulsatility Index
PV	Portal Vein
RI	Resistive Index

SD	Standard Deviation
SPSS	Statistical Package for Social Sciences
UK	United Kingdom
US	Ultrasound
USA	United States of America
WHO	World Health Organization

DEFINITION OF TERMS

Congestion index	The ratio of cross-sectional portal vein diameter to portal vein velocity.
Doppler ultrasound	Noninvasive technique used to assess blood flow in blood vessels. Vessels studied were portal vein, hepatic veins and proper hepatic artery**.** It entails color and spectral aspects.
Echogenicity	The ability to bounce an echo, e.g. return the signal in ultrasound examinations therefore echogenicity is higher when the surface bouncing the sound echo reflects increased sound waves.
Hepatofugal	Also called non-forward portal flow (NFPF). It is an abnormal flow pattern where the portal venous flow is from the periphery of the liver towards the porta and backwards along the portal vein.
Hepatopetal	Denotes flow of blood towards the liver, which is the normal direction of blood flow through the portal vein.
Homogeneous echogenicity	Uniform liver echogenicity
Hyperechoic	Generalized increase in hepatic echogenicity**.**
Portal hypertension	Hepatic venous pressure gradient (HVPG) greater than 5 mmHg. HVPG is a surrogate for the portosystemic pressure gradient. Ultrasound features of portal hypertension include hepatofugal portal vein flow, portosystemic collateral pathways, splenomegaly and ascites.

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ABSTRACT

Background: Liver cirrhosis is a chronic, progressive liver disease characterized by scarring of the liver and nodule formation. The most common causes are hepatitis and chronic alcoholism. It is ranked as the 14th most common cause of death worldwide. The clinical diagnosis of cirrhosis is based on a combination of clinical, biological and radiological findings. Hepatobiliary Doppler ultrasound is a valuable noninvasive and widely available tool in evaluating the hemodynamics and caliber of portal venous system and hepatic vessels. It helps in assessment of the severity of liver cirrhosis and complications such as portal hypertension allowing prompt intervention and prevention of further complications. Portal vein Congestive Index (CI) is a marker of increased portal pressures. However, there is underutilization and paucity of data on the role of Doppler ultrasound in our setup.

Objectives: To describe the Doppler ultrasound findings of portal and hepatic vessels and ultrasound features associated with portal hypertension in patients with clinically diagnosed liver cirrhosis.

Methods: This was a cross-sectional study conducted among adult patients with clinical diagnosis of liver cirrhosis from May 2019 to April 2020. A census sampling was used to recruit eligible participants.65 participants were studied. A data collection tool was used to record age, gender, history of alcohol consumption, jaundice, hepatitis infection titers, hepatobiliary gray scale and Doppler ultrasound findings. Mindray M7, a portable ultrasound machine with exquisite Doppler capability was used, utilizing 3.5-5 MHz curvilinear transducer (Doppler angle <60º).Continuous variables were analyzed using mean, median, and their corresponding standard deviation and interquartile ranges while categorical variables were summarized as proportions and percentages. Chi square test and Fischer's exact test were done to assess association between liver span, echogenicity and hepatofugal flow. Mann Whitney U test was done to assess the differences in the distribution of continuous variables (portal vein velocity, diameter, CI and Hepatic Artery Resistive Index) among the categorical variables (ascites, splenomegaly and hepatofugal flow). A P value of less than 0.05 was considered significant.

Results: 41/65**(**63.1%) were male. The mean age was 47 years (SD=7.8).42/65(64.6%) had liver surface irregularities and 25/65(38.5%) had hyperechoic parenchymal echogenicity. 35/65 (53.8%) had ascites while 32/65 (49.2%) had splenomegaly. 18/65 (27.7%) had hepatofugal flow. 22/65 (33.8%) had non-triphasic hepatic vein waveform. The mean portal vein velocity, portal vein diameter, CI and Hepatic Artery Resistive Index (HARI) were 13.49 cm/s, 12.73mm, 0.13 and 0.76 respectively. Increasing HARI and CI were significantly associated with hepatofugal flow ($p<0.001$,<0.001), ascites ($p=0.025$,0.001) and splenomegaly ($p=0.023$,<0.001).

Conclusion: Majority of the patients had liver surface irregularities with about half of the patients having increased main portal vein diameter. Increasing HARI and Congestive Index were significantly associated with presence of ascites, splenomegaly and hepatofugal flow.

Recommendation: There is need for routine ultrasonography evaluation with emphasis on Doppler studies of the hemodynamic changes in patients with liver cirrhosis. Prospective studies be done to further determine the strengths of association.

CHAPTER ONE: INTRODUCTION

1.1 Background information.

Liver cirrhosis is defined as chronic liver disease characterized by diffuse fibrosis and conversion of normal liver architecture into abnormal nodules as a result of complex and multifactorial process including inflammation, fibrosis and regeneration (Riahinezhad et al., 2018). It results from various mechanisms of liver injury that lead to inflammation and fibrogenesis; histologically, it's marked by diffuse nodular regeneration with surrounding dense fibrotic septa and subsequent parenchymal normal architectural loss leading to distorted hepatic vasculature. This distortion results in increased portal blood flow resistance and hence portal hypertension ensues.(Iwakiri, 2014).

Liver cirrhosis is a public health concern worldwide and a cause of morbidity and mortality. The National Center for Health Statistics (NCHS-USA) and Centers for Disease Control (CDC) estimates that in 2009, cirrhosis and chronic liver disease represented 12^{th} leading cause of death overall and 5^{th} leading cause of death for patients aged 45 to 54 years in USA (Scaglione et al., 2015). Liver Cirrhosis and its complications are one of the leading causes of death and liver transplant worldwide. (Blachier et al., 2013) . It has been noted to be a major cause of global health burden. Global Burden of Disease 2010 study, showed that liver cirrhosis lead to 1.2% (31 million) of Disability Adjusted Life Years (DALYs) and 2% (1 million) of all deaths worldwide that year (Mokdad et al., 2014).

The burden of liver cirrhosis in Sub-Saharan Africa rose to 57% in a span of 20 years, from 1990 to 2010 where liver cirrhosis deaths doubled between 1980 and 2010, from 53,000 in 1980 to 103,000 in 2010. (Mokdad et al., 2014).

In East Sub-Saharan Africa , the mortality rates per 100,000, due to liver cirrhosis in 1990, 2010 and 2017 were 13.3, 11.3 and 34.8 respectively while in Kenya, age standardized mortality rate for both sexes were 15.3 (1980), 14 (1990),12.9 (2000) and 14.5 (2010) (Mokdad et al., 2014 & Sepanlou et al., 2020).

Clinical diagnosis of liver cirrhosis is based on a combination of clinical(history taking and physical examination), biological and radiological findings (Park et al., 2017 & Sonhaye et al., 2018).

Portal blood flow, hemodynamic changes and Hepatic vein pressure gradient are crucial for the diagnosis of portal hypertension and for the evaluation of prognosis in cirrhotic patients (Sacerdoti et al., 1995).

Ultrasound is an imaging technology that utilizes high-frequency sound waves to uniquely characterize tissue. It relies on properties of acoustic physics (compression/rarefaction, reflection, impedance). The frequency of the sound waves applied in medical ultrasound ranges in millions of cycles per second (megahertz, MHz) (Klibanov et al., 2015).

An ultrasound transducer sends an ultrasound pulse into tissue and then receives echoes back. The echoes contain spatial and contrast information forming a rapidly moving two-dimensional grayscale image. Doppler ultrasound can detect a frequency shift in echoes, and determine whether the tissue is moving toward or away from the transducer hence invaluable for evaluation of structures such as blood vessels (Klibanov et al., 2015).

Doppler ultrasound is an effective method for assessment of the portal venous system to detect the direction of portal blood flow, hepatic artery and demonstrate hepatic veins' continued turbulence (Jagt et al., 1999 & Bolondi, 1991).

Doppler ultrasound is also effective for non-invasive diagnosis of intra-abdominal portosystemic shunts, especially in patients with cirrhosis (Görg et al., 2002).

1.1.1 Anatomy of the liver, the portal and systemic circulation.

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 et al., 2004). It is found in the right upper quadrant of the abdomen.

1.1.2 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.

Further subdivision into segments is based on branches of the right and left hepatic arteries. (Stephanie Ryan, 2nd Edition Anatomy for Diagnostic imaging 2004)

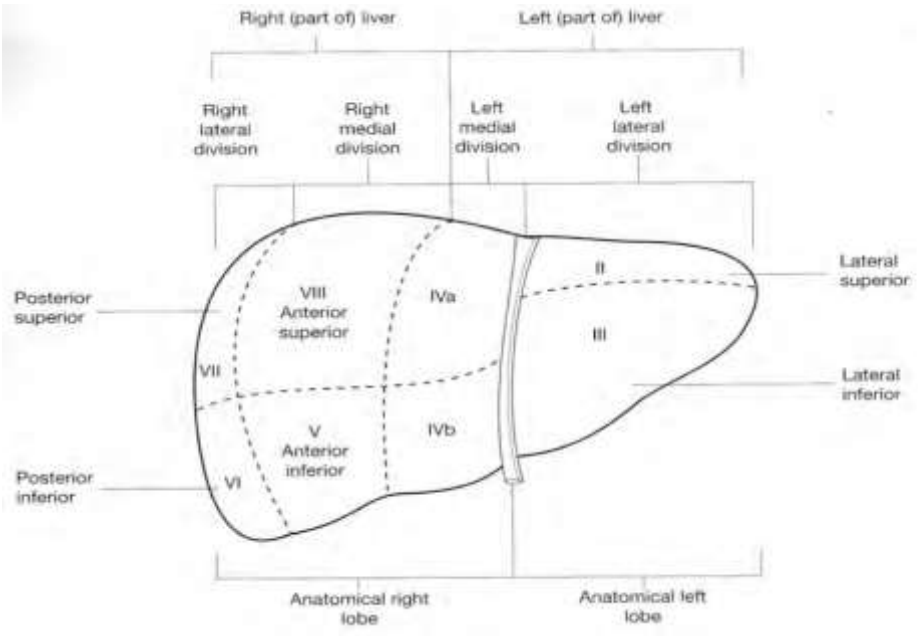


Figure 1: A diagram of Couinand's classification of the liver

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. (Stephanie Ryan, 2nd Edition Anatomy for Diagnostic imaging 2004)

1.1.3 The arterial supply of the liver

The liver receives a dual blood supply from the portal vein and hepatic arteries. The portal vein supplies ~75% of the liver's blood supply by volume and carries venous blood drained from the spleen, gastrointestinal tract, and its associated organs (hence oxygen-poor and nutrient-rich).

The hepatic arteries supply arterial blood to the liver and account for the remainder of its blood flow (hence oxygen-rich and nutrient-poor). The hepatic artery divides into approximately equal-sized right and left hepatic arteries before entering the liver at the porta hepatis

1.1.4 Venous drainage of the liver

The liver is drained by hepatic veins, which drain upwards and backwards to the IVC without an extrahepatic course. (These veins also assist in the stabilization of the liver.). Right, middle and left hepatic veins drain corresponding thirds of the liver Hepatic veins have no valves. (Stephanie Ryan, 2nd Edition Anatomy for Diagnostic imaging 2004)

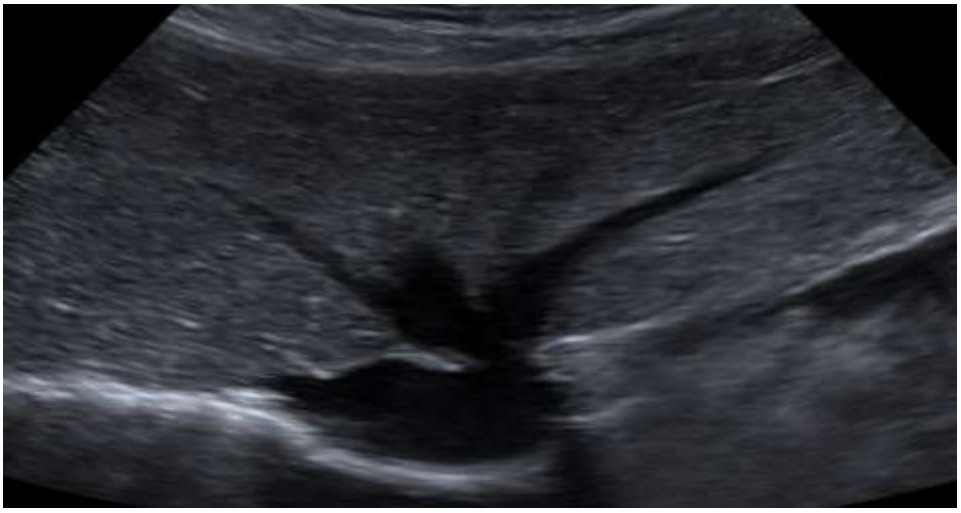


Figure 2: Transverse subcostal view demonstrates the hepatic veins draining into the IVC
Adapted from Measurement in Ultrasound by Paul S. Sidhu, 2nd Edition, Page 31

1.1.5 The portal vein

The portal vein is formed by the union of the superior mesenteric and splenic veins behind the neck of the pancreas at the level of the L1/L2 lumbar vertebra. It

receives the superior pancreaticoduodenal vein, the right gastric and left gastric (coronary) veins. It lies posterior to the common bile duct and the hepatic artery. It is separated from the IVC by the epiploic foramen. Its proximity to the IVC at this point is utilized at surgery for portosystemic venous shunting in portal hypertension. At the porta hepatis the portal vein divides into right and left branches. The right branch receives the cystic vein and the left receives the para-umbilical veins.

Within the liver the portal vein is distributed with the branches of the hepatic artery (Stephanie Ryan, 2nd Edition Anatomy for Diagnostic imaging 2004)

1.1.6 Portosystemic anastomoses

Portal venous pressure is raised when there is obstruction to blood flow in the portal vein or the hepatic veins. Portosystemic collateral pathways then open where the two systems communicate (Stephanie Ryan, 2nd Edition Anatomy for Diagnostic imaging 2004).

1.2 Problem statement

Liver cirrhosis and its complications are one of the leading causes of death and liver transplant worldwide (Blachier et al., 2013).

Gray scale hepatobiliary ultrasound has been used to describe the liver architectural changes. However, less emphasis has been on Doppler ultrasound assessment of portal and hepatic vasculature in assessing the cardinal vascular changes and probable complications of liver cirrhosis such as portal hypertension. (Berzigotti & Reverter, 2014).

Liver biopsy and hepatic venous pressure gradient measurement are the gold standards for diagnosis of liver cirrhosis and portal hypertension (PHT) respectively (Chung Wu, 2008). However both are invasive and relatively high cost while liver biopsy has been associated with sampling errors, risks of complications, patient discomfort and may yield a negative rate of up to 24% (Sonhaye et al., 2018 & M. Y. Kim et al., 2014).

There is underutilization of Doppler ultrasonography in our set up in assessment and detection of portal hypertension in liver cirrhosis. At Moi Teaching and Referral Hospital records department, in 2018, of the 56 patients with clinically diagnosed liver cirrhosis referred for hepatobiliary ultrasound, none had a requisition for Doppler ultrasound.

In our set up, diagnosis of liver cirrhosis has been based on clinical, biological and radiological findings, therefore Doppler ultrasound findings as a complimentary to the gray scale ultrasonography would aid in making the diagnosis and assessment of severity and complications (Jagt et al., 1999 & Sonhaye et al., 2018).

1.3 Justification

Doppler ultrasound being noninvasive method may be used as a follow up investigation for the vascular changes in patients with liver cirrhosis (Gerstenmaier & Gibson, 2014 & Goyal et al., 2009).

Doppler Ultrasound is safe, widely available and affordable in detection of portal or hepatic vein thrombosis and assessment of portal venous hypertension as a complication of cirrhosis (Gerstenmaier & Gibson, 2014 & Procopet & Berzigotti, 2017).

Routine ultrasound evaluation and Doppler assessment can detect the development of portal hypertension, and other complications of cirrhosis such as ascites that may have a negative effect on the patient's prognosis.

No published data in Kenya regarding Doppler ultrasonography in patients with clinically diagnosed liver cirrhosis hence there is general paucity of data in our set up on its role in assessment of portal and hepatic vessels in liver cirrhosis.

This study aims to assess the portal and hepatic vessels in clinically diagnosed liver cirrhosis and describe features associated with portal hypertension as a complication of liver cirrhosis.

There is need to develop local guidelines on use of Doppler ultrasound when assessing patients with clinically diagnosed liver cirrhosis.

1.4 Research question

What are the Doppler ultrasound findings of portal and hepatic vessels and the ultrasound features associated with portal hypertension in adult patients with clinically diagnosed liver cirrhosis?

1.5 Objectives

1.5.1 Broad Objective

To describe the Doppler ultrasound findings of portal and hepatic vessels and the ultrasound features associated with portal hypertension in adult patients with clinically diagnosed liver cirrhosis.

1.5.2 Specific objectives:

1. To describe the hepatobiliary grayscale ultrasound findings in adult patients with clinically diagnosed liver cirrhosis.
2. To describe Doppler flow patterns and indices of the portal vein, hepatic vein and hepatic arteries in adult patients with clinically diagnosed liver cirrhosis.
3. To describe ultrasound features associated with portal hypertension in adult patients with clinically diagnosed liver cirrhosis**.**

CHAPTER TWO: LITERATURE REVIEW

2.1 Introduction

Liver is the largest internal organ in the body, accounting for approximately 2% to 3% of the total body weight of an adult (Skandalakis et al., 2004). It has homeostatic functions including detoxifying harmful substances in the body, synthesis of most coagulation factors and inhibitors and fibrinolytic factors. It is crucial to have a balance between the anticoagulant and pro-coagulant factors and advance in liver disease leads to defective hemostatic function of the liver (Zocco et al., 2009).

Liver cirrhosis is defined histologically as a diffuse hepatic process characterized by fibrosis and conversion of the normal liver architecture into structurally abnormal nodule (Pinzani et al., 2011).

However, reversal of cirrhosis (in its earlier stages) has been documented in several forms of liver disease following treatment of the underlying cause. Patients with cirrhosis are susceptible to a variety of complications, and their life expectancy is markedly reduced (Nusrat et al., 2014).

Portal hypertension is defined as elevated pressures in the portal venous system with hepatic venous pressure more than 5 mm Hg greater than the inferior vena cava pressure (Banerjee, 2012).

Liver cirrhosis is the most common intrahepatic cause of portal hypertension and accounts for 90% of portal hypertension (Rumack et al., 2011).

2.2 Epidemiology

Chronic liver disease occurs irrespective of age, sex, region or race. Liver cirrhosis characterized by fibrosis, architectural distortion and formation of regenerative nodules is an end result of a majority of liver diseases. Cirrhosis is an increasing cause of morbidity and mortality in more developed countries, being ranked as the 14th most common cause of death worldwide (Sepanlou et al., 2020).

World Gastroenterology Organization, 2001, estimated worldwide mortality from cirrhosis was 771,000 people, ranking 14th and 10th as the leading cause of death in the world and in developed countries, respectively. It was speculated that by 2020, cirrhosis would rise to be the 12th leading cause of death.

Global Burden of Disease 2010 study, showed that liver cirrhosis lead to 1.2% (31 million) of Disability Adjusted Life Years (DALYs) and 2% (1 million) of all deaths worldwide that year, with almost equal proportions attributable to excessive alcohol consumption, hepatitis B and C viral infections (Mokdad et al., 2014). Prevalence of cirrhosis and other chronic liver diseases was noted to increase by 12.4% from 2006-2016, and being the cause of 1,256,900 deaths in 2016 (Sepanlou et al., 2020).

According to (Byass, 2014) it was noted that globally, deaths because of liver cirrhosis had increased from 676,000 in 1980 to over 1 million in 2010.

According to National Statistics in United Kingdom, liver diseases have been categorized as the 5th common cause of death. Chronic liver disease and cirrhosis lead to about 35,000 deaths each year in the United States, with cirrhosis being the 9th cause of death whereas liver diseases in general, being the 2nd leading cause of mortality among all the digestive diseases in the USA. There is marked geographical variations in the rates of morbidity and mortality due to cirrhosis (Rowe, 2017).

The burden of liver cirrhosis in Sub-Saharan Africa rose to 57% in a span of 20 years, that is from 1990 to 2010 with a 34% attribution to hepatitis B infection, 18% and 17% attributed to alcohol consumption and Hepatitis C infection respectively (Mokdad et al., 2014).

In sub-Saharan Africa, liver cirrhosis deaths doubled between 1980 and 2010, from 53,000 in 1980 to 103,000 in 2010, with about half as high cirrhosis mortality rates in southern sub-Saharan Africa as compared to the central, eastern, and western regions of Africa. This pattern is consistent with the distribution of hepatitis B and C infection. Cirrhosis mortality rates in the Central Africa Republic, Gabon, Malawi, Uganda and Cote d'Ivoire ranked in the highest tenth percentile globally in 2010. (Mokdad et al., 2014).

Western, eastern, and central sub-Saharan Africa had the next highest, after central Asia, age standardized death rates due to liver cirrhosis for both sexes combined in 2017, with rates of 35.8 per 100 000 population in western Africa, 34.8 per 100 000 population in eastern Africa, and 34.3 per 100 000 population in central sub-Saharan Africa (Sepanlou et al., 2020).

In East Sub-Saharan Africa , the mortality rates per 100,000, due to liver cirrhosis in 1990, 2010 and 2017 were 13.3, 11.3 and 34.8 respectively while in Kenya ,age standardized mortality rate for both sexes were 15.3 (1980), 14 (1990),12.9 (2000) and 14.5 (2010) with percent changes of -4.8% from 1980 to 2010 and 3.7% from 1990 to 2010 (Mokdad et al., 2014 & Sepanlou et al., 2020).

2.3 Risk factors

Cirrhosis is a late stage of scarring of the liver caused by many forms of liver diseases and conditions, such as hepatitis and chronic alcoholism. The progression of liver injury to cirrhosis may occur over weeks to years (Stasi et al., 2015).

The development of liver cirrhosis from the chronic liver disease is influenced by number of factors. Understanding these factors is key in personalizing the management of the patient (Wiegand & Berg, 2013).

There are multiple etiologies of liver, disease that can result in cirrhosis, either by causing chronic hepatic inflammation or cholestasis. The most common causes of cirrhosis in the Germany are hepatitis B and C, alcoholic liver disease, and nonalcoholic liver disease, which cumulatively accounts for majority of patients on the liver transplantation (Wiegand & Berg, 2013).

There are differing geographical distribution of the major risk factors which includes; heavy alcohol consumption, chronic viral hepatitis B and C infections, obesity, autoimmune hepatitis, primary sclerosing cholangitis and other metabolic diseases. Evolution of these risk factors aids in better understanding and prediction of future burden of liver disease (Rowe, 2017). The global health community is emphasizing on the need to control these risk factors especially the alcohol intake and viral hepatitis infection (Mokdad et al., 2014).

2.4 Diagnosis

Diagnosis of liver cirrhosis is made following a detailed history taking, thorough physical examination, laboratory work ups, imaging and histopathological assessment of liver biopsy. Clinical diagnosis of liver cirrhosis is based on clinical, biological and radiological findings. Clinical entity entails history taking and physical examination (Sonhaye et al., 2018).

The history may reveal any risk factors such as alcohol consumption. Clinical manifestations of cirrhosis include nonspecific symptoms such as anorexia, weight loss, weakness, fatigue or signs and symptoms of hepatic decompensation (jaundice, pruritus, signs of upper gastrointestinal bleeding, abdominal distension from ascites, and confusion due to hepatic encephalopathy.

Patients with compensated cirrhosis may be asymptomatic or report nonspecific symptoms while patients with decompensated cirrhosis may present with jaundice, pruritus, signs of upper gastrointestinal bleeding (hematemesis, melena and hematochezia), abdominal distension or confusion. Female patients may have chronic anovulation, which manifest as amenorrhea or irregular menstrual bleeding.

Physical examination would elicit; pallor, jaundice, redness of palm, hepatomegaly, splenomegaly, ascites and features of stigmata of chronic liver disease such as digital clubbing, hypertrophic osteoarthropathy, Dupuytren's contracture, leuconychia, gynecomastia, testicular atrophy, loss of pubic hair, spider angiomata (spider telangiectasias), gynecomastia, caput medusa, and asterixis (bilateral but asynchronous flapping motions of outstretched, dorsiflexed hands).

Patients often have a decrease in mean arterial pressure and this contributes to the development of hepatorenal syndrome and is an important predictor of survival (Velez et al., 2015)

The laboratory work ups entails; full hemogram, coagulation profiles, albumin, liver function tests. The Aspartate and Alanine aminotransferases are moderately elevated. AST is more often elevated than ALT. As chronic hepatitis progresses to cirrhosis, AST / ALT ratio becomes more than 1. Alkaline Phosphatase increases but by less than two to three folds the upper normal limit. Levels of GGT are typically much higher in chronic liver disease from alcohol than other causes.

Bilirubin levels may be normal in well-compensated cirrhosis but tend to rise as the cirrhosis progresses. Albumin levels fall as the synthetic function of the liver declines with worsening cirrhosis (Walayat et al., 2017). Serum albumin levels help grade the severity of cirrhosis (Bernardi et al., 2020).

Coagulation profiles especially the prothrombin time increases as the ability of cirrhotic liver to synthesize clotting factors is impaired. Worsening coagulopathy correlates with the severity of hepatic dysfunction (Harrison, 2018).

Hematological abnormalities include varying degrees of cytopenia. Thrombocytopenia is the most common hematologic abnormality, while leukopenia and anemia develop later in the disease course. Thrombocytopenia is mainly caused by portal hypertension due to sequestration of platelets by congestive splenomegaly or decreased thrombopoietin (Sigal et al., 2016).

Imaging techniques include upper gastrointestinal endoscopy, hepatobiliary ultrasonography, MRI or CT scan of the abdomen, elastography and radionuclide imaging (National Institute of Diabetes and Digestive and Kidney Diseases - USA).

Hepatobiliary ultrasonography is typically the first radiological study performed because it is readily available, non-invasive, lacks ionizing radiation and affordable (Procopet & Berzigotti, 2017). It describes the liver parenchymal architecture, liver size and presence or absence of nodules, with complimentary Doppler ultrasonography for assessment of portal and hepatic vasculature.(E. C. F. Dietrich, 2010).

In advanced cirrhosis, the liver may appear shrunken and nodular. Surface nodularity, irregularities and increased parenchymal echogenicity are consistent with cirrhosis, but can also be seen with hepatic steatosis (Lelio, n.d.1989).

Typically, there is hypertrophy of caudate and lateral segments of left liver lobe and atrophy of posterior segments of the liver lobe with a caudate to right lobe ratio of greater than 0.65 suggesting presence of cirrhosis. However, its sensitivity is poor (Merzan et al., 2017).

Ultrasonography may also be used as a screening test for hepatocellular carcinoma and portal hypertension. Presence of nodules on ultrasonography warrants further investigation since benign and malignant nodules have indistinguishable ultrasonography characteristics (Kelly et al., 2018).

Doppler imaging findings of increased portal vein diameter, the presence of collateral veins, and decreased portal circulation flow may suggest portal hypertension (McNaughton & Abu-Yousef, 2011).

Ultrasound features of portal hypertension includes biphasic or reversed portal vein flow, Para umbilical vein recanalization, portal-systemic collateral pathways, splenomegaly and ascites (https://radiopaedia.org/articles/portal-hypertension).

Elastography assesses liver stiffness by applying mechanical waves and measuring their propagation speed through tissue using imaging. Increasing scarring of the liver is associated stiffening and fibrosis. Modality options include ultrasound (transient elastography [TE], acoustic radiation force impulse imaging [ARFI], two-dimensional [2D] shear wave elastography [SWE]), and MRI (magnetic resonance elastography [MRE]) (Zhang et al., 2020).

Liver biopsy is considered the gold-standard diagnostic method to identify the typical features of cirrhosis hence the definitive test (Procopet & Berzigotti, 2017 & Sonhaye et al., 2018). However, liver biopsy is not required if the clinical, laboratory, and radiologic data strongly suggest the diagnosis of liver cirrhosis and if the results would not influence change in the patient's management (Sumida et al., 2014).

Hepatic venous pressure gradient measurement is the gold standard for diagnosis of portal hypertension (PHT) (M. Y. Kim et al., 2014). HVPG is more predictive of clinical decompensation of cirrhosis than histological fibrosis staging. Findings from HVPG measurements may be predictive of new or recurrent bleeding that help in determining the effectiveness of pharmacologic therapy. Additionally, in patients with cirrhosis, the HVPG can predict the development of varices, ascites, encephalopathy, or other complications. A decrease in the HVPG is related to a reduction in the incidence of varices and variceal hemorrhage. Therefore, HVPG measurement, besides monitoring hemodynamic effects, will mainly assess the all aspects and spectrum of chronic liver diseases (Suk, 2014).

2.5 Pathophysiology

2.5.1 Pathophysiology of liver cirrhosis

The liver is normally capable of regenerating damaged cells but with continued exposure to factors that damage the liver such as alcohol consumption and chronic viral infections, there is resultant liver injury, chronic liver disease and scarring hence liver cirrhosis. The transformation from chronic live disease to cirrhosis involves inflammation, angiogenesis and parenchymal extinction lesions caused by vascular occlusion (Schuppan et al., 2008).

Cirrhosis leads to liver shrinkage and hardening making it difficult for efficient nutrient- rich blood supply into the liver from both portal vein and hepatic arteries and impaired venous drainage via the hepatic veins. The hepatic microvasculature changes become pronounced characterized by sinusoidal remodeling, formation of intrahepatic shunts and hepatic endothelial dysfunction with resultant insufficient release of vasodilators especially nitric oxide which in turn activates increased production of vasoconstrictors (Schuppan et al., 2008).

Portal venous flow velocity is decreased, due to increased hepatic resistance to portal blood flow in a cirrhotic liver. This follows structural dysfunction of the liver due to advanced liver disease and functional abnormalities leading to endothelial dysfunction, increased hepatic vascular tone, portal vein pressure rise and eventually portal hypertension. Development of high blood pressure within the portal vein consequently causes a backup of blood leading to esophageal varices that may rupture and bleed. Portal venous blood flow becomes reversed with advanced portal hypertension. Reversed flow is also demonstrated in patients with veno-occlusive disease of the liver and portosystemic shunts (Jagt et al., 1999).

Subsequently, angiogenesis contributes to the arterialization at the portal tracts with increased development of intra-hepatic arterio-venous shunts which effectively bypass the parenchyma. Blood flows preferentially through these vascular channels due to the relative low resistance of these shunts and leaves the remainder of the hepatic parenchyma devoid of appropriate blood flow leading to hepatocyte dysfunction.

The level of fibrosis with subsequent absence of hepatic tissue compliance and hypertrophy of cells exerts a possible compression over hepatic vein due to low stretching liver capsule leading to changes in waveform and decreasing phasic oscillations (Bolondi, 1991 & Sonhaye et al., 2018).

Liver cirrhosis is often asymptomatic, inert and unsuspected until complications are present or decompensation occurs. Diagnosis of the asymptomatic cases is usually made when incidental screening tests such as laboratory investigations or radiological findings. However, a few patients present at already complicated stage. Complications of liver cirrhosis include portal hypertension, variceal bleeding, spontaneous bacterial peritonitis, liver failure, hepatic encephalopathy, hemorrhoids or ascites (Schuppan et al., 2008).

Major complications of cirrhosis include; portal hypertension, variceal hemorrhage, ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, hepatocellular carcinoma, hepatorenal syndrome, hepatopulmonary syndrome and liver failure (Nusrat et al., 2014).

2.5.2 Pathophysiology of portal hypertension

Portal hypertension describes elevated pressures in the portal venous system. It may be caused by intrinsic liver disease, obstruction, or structural changes that result in increased portal venous flow or increased hepatic resistance. The resistance causes increased pressure, resulting in varices or dilations of the veins and tributaries.

Pressure within the portal system is dependent upon both input from blood flow in the portal vein, and hepatic resistance to outflow. Normal portal vein pressures range from 5–10 mm Hg (Banerjee, 2012).

Portal hypertension is the most common complication of liver cirrhosis and subsequent mortality, with esophageal varices being its first consequence. A good marker of portal hypertension is hepatic vein pressure gradient (Iwakiri, 2014).

Splanchnic vasodilation occurs as an adaptive mechanism to the changes in the intrahepatic hemodynamics and impaired hepatic vascular tone which together with the portal hypertension play major role in development of hepatorenal syndrome and ascites that are complications of liver cirrhosis. Compensatory systemic vasodilation causes pulmonary ventilation- perfusion mismatch that would lead to hepatopulmonary syndrome and arterial hypoxemia (Schuppan et al., 2008).

There is association of intrahepatic veins thrombosis, progression of liver cirrhosis and occlusion of the small sized intrahepatic veins and sinusoids stimulating their capillarization and this acts as potential triggering factor for liver cells and tissues remodeling (Zocco et al., 2009).

High resistive index of the hepatic artery is seen in patients with end-stage liver disease, though mostly in children with severe cirrhosis secondary to biliary atresia (Jagt et al., 1999).

Portal hypertension is a multifactorial based syndrome rather than as a result of anatomical, fixed or increased intrahepatic vascular resistance. It is considered as the sum of functional and structural abnormalities both in the liver and splanchnic circulation resulting from both increase in portal collateral venous blood flow and intrahepatic vascular resistance (IHVR). IHVR occurs due to tissue scarring,

regenerative nodular formation and endothelial dysfunction with resultant vascular obliterative process. Splanchnic vasodilation with increased mesenteric and splenic blood flow plays a role maintaining the portal hypertension. Worsening portal hypertension causes angiogenesis and fibrogenesis leading to new vessel formation hence development of portosystemic collaterals (Vorobioff & Groszmann, 2017).

Complications of portal hypertension include; ascites, hepatic encephalopathy, variceal hemorrhage, spontaneous bacterial peritonitis, hepatorenal syndrome, portal hypertensive gastropathy, hepatic hydrothorax, hepatopulmonary syndrome, portopulmonary hypertension and cirrhotic cardiomyopathy (Zardi et al., 2010).

Hepatofugal flow is both a specific sign and has a high predictive value for presence of portal hypertension and continuous reversed portal vein flow is associated with portosystemic shunts (Gerstenmaier & Gibson, 2014) therefore analysis of the direction of flow in the portal vein is strongly warranted in assessing portal hypertension (Görg et al., 2002).

Splenomegaly is the most common and sensitive sign of portal hypertension and acts as an independent predictor of esophageal varices and marker of clinically significant portal hypertension (CSPH) while ascites is the most common feature of clinically decompensated cirrhosis and holds significant prognostic factor (Berzigotti & Reverter, 2014).

2.6 Hepatobiliary Gray scale ultrasound findings

The liver, being a solid organ is suitably examined by ultrasound and it is seldom covered by gas-containing bowel. It has a smooth contour and as 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 (E. C. F. Dietrich, 2010).

Ultrasound based diagnosis of liver cirrhosis is attributed to both hepatic and extrahepatic signs. The extrahepatic signs include ascites and splenomegaly whereas hepatic signs are either indirect signs such as enlarged liver and hypertrophy of the caudate liver lobe, in the early stages, while in late stages of cirrhosis, the liver may shrink significantly. Disproportionate segmental atrophy and hypertrophy are also typical (J. Dietrich, 2002 & Schuppan et al., 2008).

Subjective signs include diffuse liver parenchymal hyper-echogenicity due to fatty infiltration of the liver or inhomogeneous or coarse echo pattern, irregular surface outline, focal nodularity and increased caudate-to-right liver lobe size ratio(Lelio, n.d. 1989 & Iranpour et al., 2015). However, parenchymal echogenicity has better prediction of liver cirrhosis as compared to liver surface nodularity (Gerstenmaier & Gibson, 2014).

Gray scale hepatobiliary sonography only indicates the irregularities of the liver surface and poorly visualized hepatic veins consistent with liver cirrhosis but this is found in only 50% of the patients (Herbay et al., 2000).

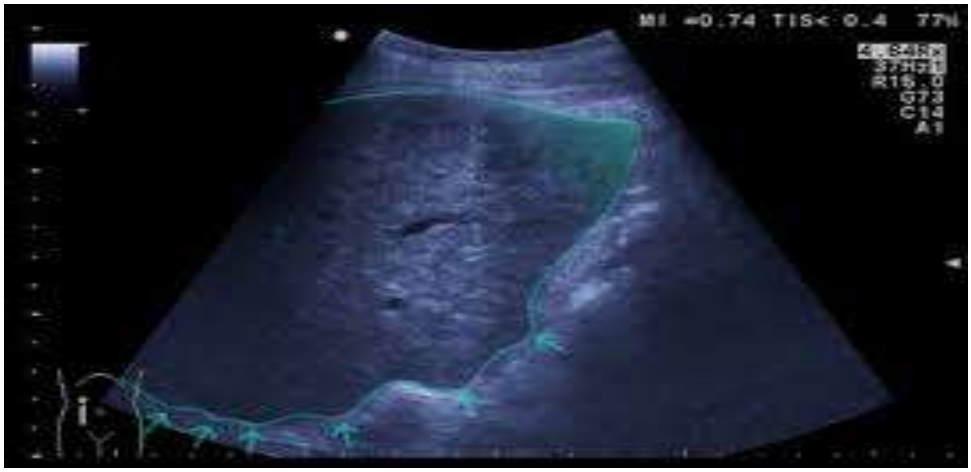


Figure 3: **Transverse subcostal view demonstrates heterogeneous, coarse parenchyma with blunted and nodular liver margins.**
Adapted from https://www.amboss.com/us/knowledge (Center for Internal Medicine, St. Hedwig Hospital, Berlin)

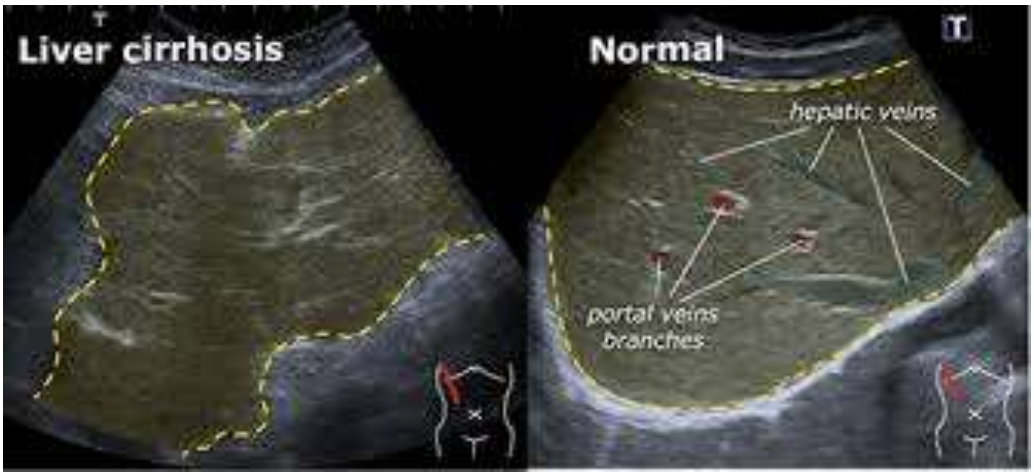


Figure 4: Transverse subcostal view demonstrates Liver cirrhosis versus normal liver parenchyma
Adapted from https://www.startradiology.com (Leiden University Medical Center)

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 et al., 1991).Therefore, ultrasound can provide a non-invasive prediction of liver histology which in moderate fibrosis and established cirrhosis can be both highly sensitive and specific.

Examination Criteria

When assessing the liver, the following aspects are assessed: size, shape, outline, texture/echogenicity and measurements are taken (E. C. F. Dietrich, 2010).

Size

The size of the liver has been measured using many methods, including 3D-reconstructions. Liver size measurement has however been found not to have an impact in daily routine because there is no reliable and reproducible ultrasound method established so far. The largest craniocaudal diameter (midclavicular line) is taken (Patzak et al., 2014).

Shape

Liver is normally described to be pyramidal in shape.

Outline, surface.

The normal liver surface should be smooth with no indentations or protrusion of lumps. The inferior border of the liver in a 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. When comparing the echogenicity of the liver to that of the spleen and renal cortex, the examination should be done at the same depth.

Liver surface and vessels' borders are smooth and vascular architecture has a classic dichotomy in branching.

Hepatic veins

The three hepatic 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, however the 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.

2.7 Doppler ultrasound

Doppler ultrasound has been in used since the 1950s though the Doppler Effect was first described by Christian Andreas Doppler, an Austrian mathematician and physicist in 1880. Doppler ultrasound velocimetry uses the Doppler principle to analyze the properties of the blood flow in a vessel of interest. This explains the observed change in wave frequency relative to the speed of a moving object. In Doppler ultrasonography, the emitted ultrasound frequency will change when ultrasound beam encounters moving blood. The underlying principle is that when sound or light waves are moving between a transmitter and a receiver which are stationary in relation to each other, then the receiver will register the same frequency as the transmitter emitted. If there is relative movement towards each other than the receiver will register a slightly higher frequency (shorter wavelength) than was transmitted; conversely if there is relative motion apart, then the receiver will register a slightly lower frequency (longer wavelength). These small changes are known as Doppler shifts and can easily be measured by modern ultrasound equipment through direct comparison of the returning frequency with the transmitted frequency.

The derivation of the Doppler equation used in medical ultrasound is;

$$Fd = Ft - Fr = 2FtvcosQ/c$$

Fd- is the frequency or Doppler shift, Ft is the transmitted frequency, Fr is the received frequency. V is the velocity of the reflector (usually blood in the vessels). Q is the angle between the direction of flow of blood and c is the mean velocity of sound in tissues, 1540m/s. using modern ultrasound equipment the only variable which is unknown is the velocity of the reflecting blood cells.

The principle can be applied using different ultrasound modalities such as continuous-wave Doppler, pulsed-wave Doppler, color and power Doppler wave. Color Doppler is used to map the vessels to be examined while spectral Doppler provides a more detailed analysis, enabling calculation of the various indices. In addition to these indices, the flow waveform may be described or categorized by the presence or absence of a particular feature, for example the absence of end-diastolic flow and the presence of a post-systolic notch.

Duplex Doppler combine real time imaging with pulsed Doppler. This allows the operator to identify a specific segment in a particular vessel and to place the gate, or sample volume, at a specific location so that the source of the Doppler signal is known. In addition to transmitting the Doppler information as an audio signal, it can also be displayed as a spectral trace, or waveform scrolling across the screen (Hedrick.Pdf, n.d.).

Doppler ultrasonography is a noninvasive technique used to asses both the portal and hepatic vessels of the hepatobiliary system (Iranpour et al., 2015). The various parameters of hepatic vasculature assessed include; hepatic artery velocity and resistive index, portal vein flow direction, diameter, velocity, congestive index and hepatic artery – to - portal vein velocity ratio and hepatic vein waveforms. Main role of Doppler ultrasound being assessment of portal hypertension as a complication of liver cirrhosis (Gerstenmaier & Gibson, 2014).

Use of color Doppler sonography to detect the direction of portal blood flow aids in diagnosis of intra-abdominal shunts and indicate presence of portal vein thrombosis. The presence of portosystemic shunts and abnormal flow of blood within hepatic and portal vessels are additional indicators for cirrhosis and would depict development of portal hypertension (Herbay et al., 2000).

Doppler ultrasound is a very useful complementary tool in evaluating the haemodynamic changes and variations observed within a cirrhotic liver. Previous studies have shown that variation in hepatic haemodynamics demonstrated in liver cirrhosis tend to correlate with the severity of cirrhosis (Afif, 2017).

2.7.1 Portal vein Doppler

The portal vein is visualized in the longitudinal axis from the splenomesenteric junction to the liver hilum and the greatest anteroposterior diameter is measured at the site where the hepatic artery crosses the portal vein (Radiology Assistant).

Normal portal vein diameter is considered to be 11 ± 2 mm(Phillips, n.d.) while portal vein velocity ranges from 16–40 cm/sec. (McNaughton & Abu-Yousef, 2011).

However, portal vein velocity increases after a meal and during inspiration and decreases after exercise and on upright position (Rumack et al., 2011).

Portal vein congestion index (CI) is the ratio between the cross-sectional area of the vessel (cm2) and the blood flow (cm/s) in the portal vein. The congestion index considers the increased crossectional area of the portal vein and the significant reduction in blood flow velocity in both liver cirrhosis and portal hypertension (Jagt et al., 1999).

Congestion index (CI) of the portal vein is determined as follows:

Portal vein area = diameter A x diameter B x $\pi/4$

Flow velocity = 0.57 x maximum portal vein velocity (angle $\leq 60°$)

CI = vein area/flow velocity

The normal portal vein congestive index is 0.070 ± 0.029 cm/sec and increases to 0.171 ± 0.075 cm/sec in patients with portal hypertension.(Moriyasu et al., n.d.).

Portal vein congestion index is a marker of portal hypertension based on tendency of average portal diameter to increase as the velocity decreases. Though low portal vein velocity solely is not a useful sign of portal hypertension and the velocities are

variable and in cases of portosystemic diversion, the portal vein diameter tends to decrease to its normal size (Sonhaye et al., 2018).

Assessment of portal venous flow pattern is also crucial in diagnosing portal hypertension. Normal flow is continuous and hepatopetal with minimal variations secondary to the cardiac flow and respiration. Hepatofugal flow, however, follows a higher intrahepatic resistance compared to the resistance of portosystemic collaterals (Gerstenmaier & Gibson, 2014).

Larger portosystemic collaterals may develop in some patients presenting with a lesser resistance to the flow and drainage of large amounts of blood from one section of portal venous system or the entire portal flow (Zocco et al., 2009).

Portal venous flow tends to increase after a meal and is accompanied by decreased diastolic flow in the hepatic artery (Martínez-Noguera et al., 2002).

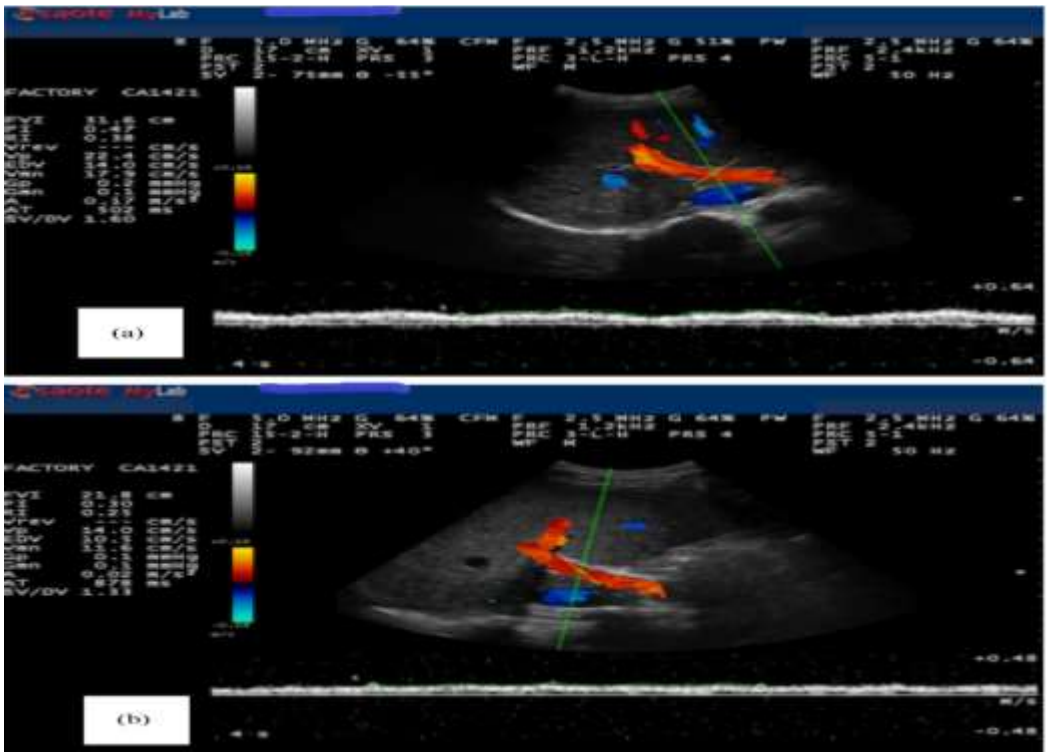


Figure 5: Flow and spectrum of portal vein

(a) In a non-cirrhotic patient, hepatopetal flow and normal mean velocity (17.9 cm/s); (b) in a cirrhotic patient, hepatopetal flow and decreased mean velocity (11.6 cm/s).

2.7.2 Hepatic vein Doppler

Normal hepatic vein waveform is triphasic indicative of an atrial systole, ventricular systole and atrial diastole, or brought about by the two periods of forward flow in each cardiac cycle, corresponding to the two phases of right atrial filling and a single period of normal transient reversed flow due to contractions of the right side of the heart and monophasic pattern of flow may be created by the deposition of fat in the liver and the inflammatory or fibrotic changes in the liver (J. Dietrich, 2002) and in individuals suspected to have liver cirrhosis, the pattern tends to be biphasic or monophasic (Gerstenmaier & Gibson, 2014).

The normal hepatic vein demonstrates a multiphasic waveform because of its proximity to the heart and the transmitted cardiac cycle (Wood et al., 2010).

In a cirrhotic liver, the fibrosis causes decreased hepatic parenchyma compliance resulting in decreased size of hepatic veins and demodulation or decrease in pulse (Sonhaye et al., 2018). Spectral abnormalities were noted by (Bolondi, n.d. 1991& Colli et al., 1994) at 50 % and 75% respectively in patients with liver cirrhosis.

Measurements should be taken in the right and middle hepatic veins to avoid artefact from transmitted cardiac movement seen in the left hepatic vein. (Goyal et al., 2009)

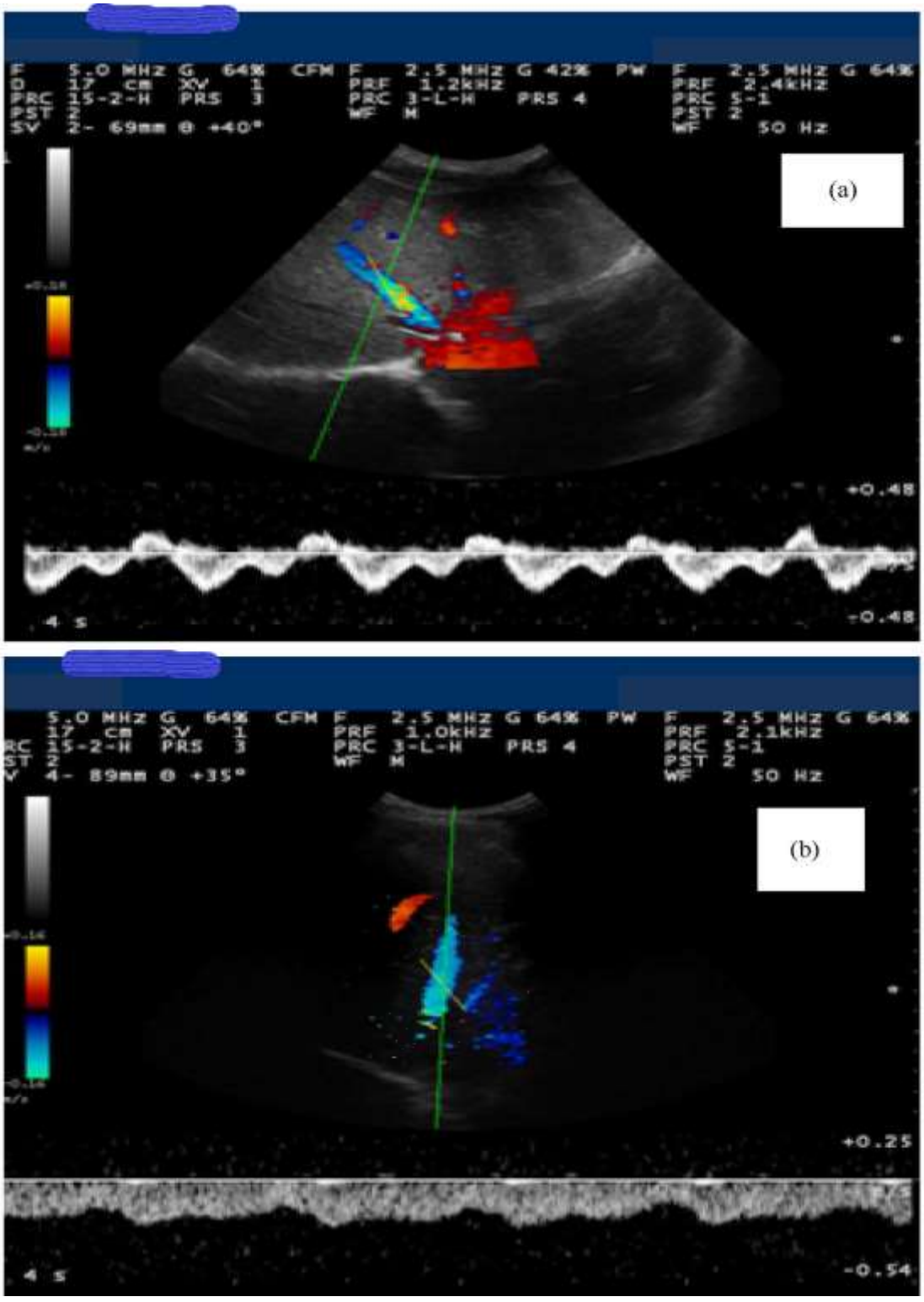


Figure 6: Hepatic vein spectrum

(a) Normal waveform in a non-cirrhotic patient characterized by a triphasic flow; (b) abnormal hepatic flow pattern in a cirrhotic patient characterized by a flat flow pattern.

2.7.3 Hepatic artery

Color Doppler ultrasonography offers a greater advantage of visualization of intrahepatic arterial vessels such as left and right hepatic arterial branches or more distal vessels. Both PI and RI are better indices for ascertaining resistance.

The normal hepatic artery has persistent flow in diastole, consequently, low distal impedance of the hepatic circulation. As the blood reaches the smaller sized distal branches, the flow velocity across the lumen approaches a parabolic form giving rise to an even distribution of the Doppler shift frequencies and hence filling-in of the spectral display with subsequent increase in downstream impedance and decline in the diastolic flow. This downstream impedance can be estimated by use of the resistive index (RI) that relates the frequency shift in the lowest part of diastole to peak systole. Increasing resistance in the arterial bed will increase the pulsatility of the curve and increase the RI. RI is calculated by a simple formula of (peak systolic velocity-end diastolic velocity/peak systolic velocity) (Jagt et al., 1999).

The normal hepatic artery shows a rapid systolic upstroke with a time-to-maximum systole less than 100 milliseconds and continuous diastolic flow with RIs between 0.55 and 0.80(Wood et al., 2010).

A higher hepatic artery resistance is noted in liver cirrhosis as a result of reduced vascular space secondary to hepatic architectural distortion and constriction of arterioles by hepatic venous outflow obstruction through a feedback loop mechanism initiated by abnormal sinusoidal pressure elevation , decreased tissue oxygen tension and fluid transudation into the extravascular spaces (Morenot et al., 1967). Hepatic arterial resistance occurs parallel to that of portal venous resistance (Sacerdoti et al., 1995).

The hepatic artery maximum systolic rate increases in cirrhotic patients. As the systolic velocity increases, the diastolic velocity may decrease resulting in increased hepatic artery blood flow and the increased flow further leads to increase in arterial resistance and rise in pulse indices where both the PI and RI are noted to increase significantly (Sonhaye et al., 2018).

However HARI also increases after a meal (Rumack et al., 2011).

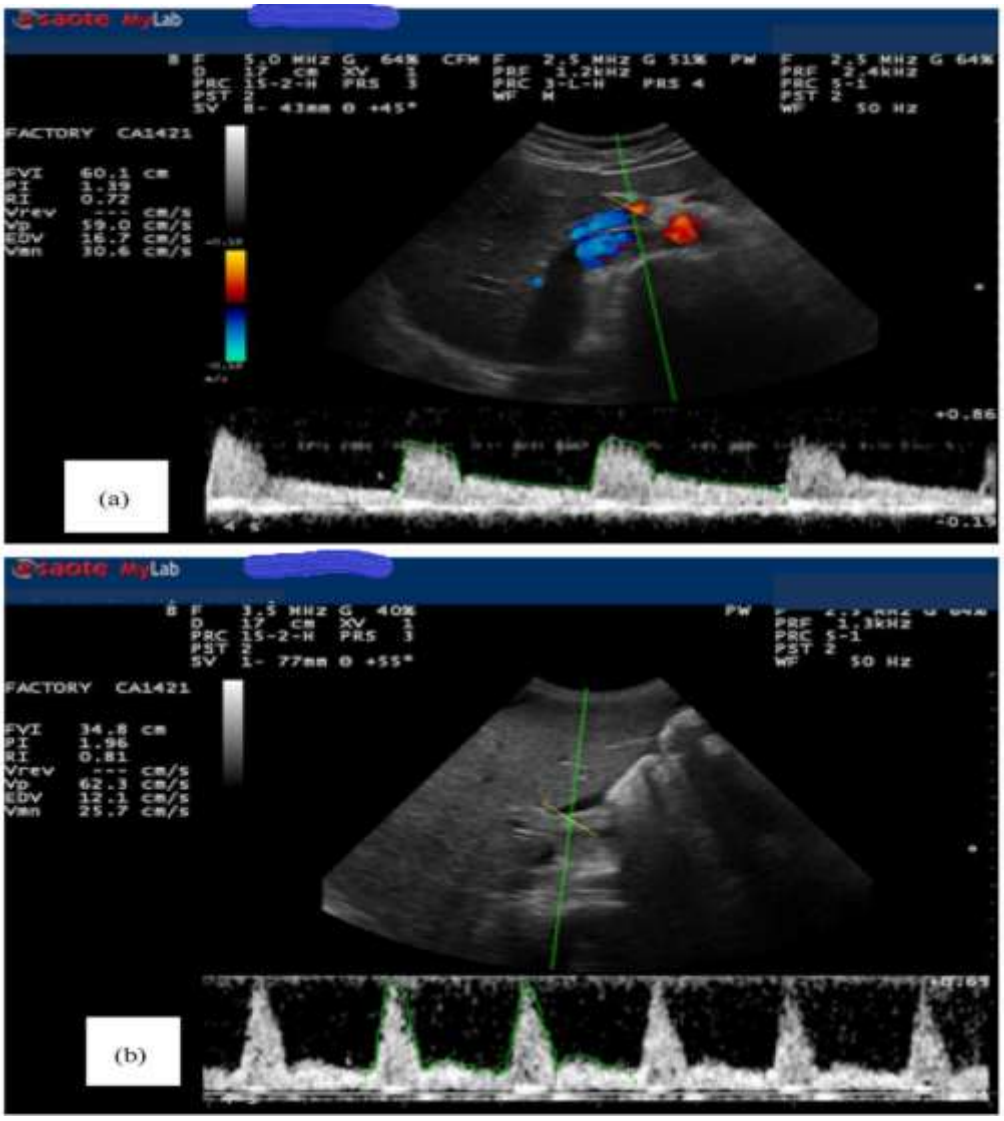


Figure 7: Hepatic artery spectrum

(a) In a non-cirrhotic patient, the RI is 0.72; (b) in a cirrhotic patient, the RI is 0.81.

CHAPTER THREE: METHODOLOGY

3.1 Study site

The study was conducted at the ultrasound room in the Radiology and Imaging department, Medical and Surgical wards / clinics at Moi Teaching and Referral Hospital (MTRH).

The Hospital is located in Eldoret town, the headquarter of Uasin Gishu county, which is 350 Kilometers Northwest of the Capital Nairobi. MTRH is a tertiary (level 6) health facility and the second National referral hospital serving as a teaching hospital for Moi University School of Medicine (MUSOM), School of nursing, Public health and Dentistry. Others 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.

Its catchment includes the Western and North Rift parts of Kenya which is roughly about 20 million people. The hospital has a bed capacity of over 700 patients, with several departments which include, radiology and imaging, surgery, pediatrics, medicine, obstetrics and gynecology, accident and emergency department among others (www.mtrh.or.ke/).

MTRH has several specialist clinics including the gastrointestinal/ liver clinic and availability of gastroenterologists and hepatologist who effectively run these clinics.

MTRH also has effective Ultrasound facilities with Doppler capabilities and available consultant radiologists thus providing standard healthcare.

3.2 Study Design

This was a descriptive cross-sectional study done over a period of one year from May, 2019 to April, 2020.

3.3 Study population

The study population was adult patients referred for hepatobiliary ultrasound, from the medical and surgical wards / clinics with clinically diagnosed liver cirrhosis at MTRH.

3.4 Eligibility criteria:

3.4.1 Inclusion Criteria

1. Adult (18 years and above) patients with clinically diagnosed liver cirrhosis.
2. Patients who consented to the study.

3.4.2 Exclusion Criteria

1. Patients with a history of previous hepatobiliary surgery.
2. Patients who declined to give consent.

3.5 Sample size determination and sampling

Based on Fisher et.al (1998) formula:

$$n = \frac{z2\ p\ (1-p)}{d^2}$$

n = desired sample size.

z = Standard normal variance equivalent to 1.96.

p = prevalence rate of spontaneous hepatofugal portal flow in liver cirrhosis is 8.3% (Bassi, 1991)

d= the desired level of significance.

When this formula is applied at d = 0.05, z = 1.96, and p = 0.083

$$n = \frac{(1.96)2 \times 0.083\ (1-0.083)}{(0.05)^2}$$

Therefore, a sample size of 117 was proposed.

However, during the year of study, a total of 67 patients with clinically diagnosed liver cirrhosis were seen and referred for hepatobiliary ultrasonography assessment. Hence, a census methodology was used to recruit all eligible participants into the study and sample size of 65 patients was attained during the period of study.

3.6 Study procedure

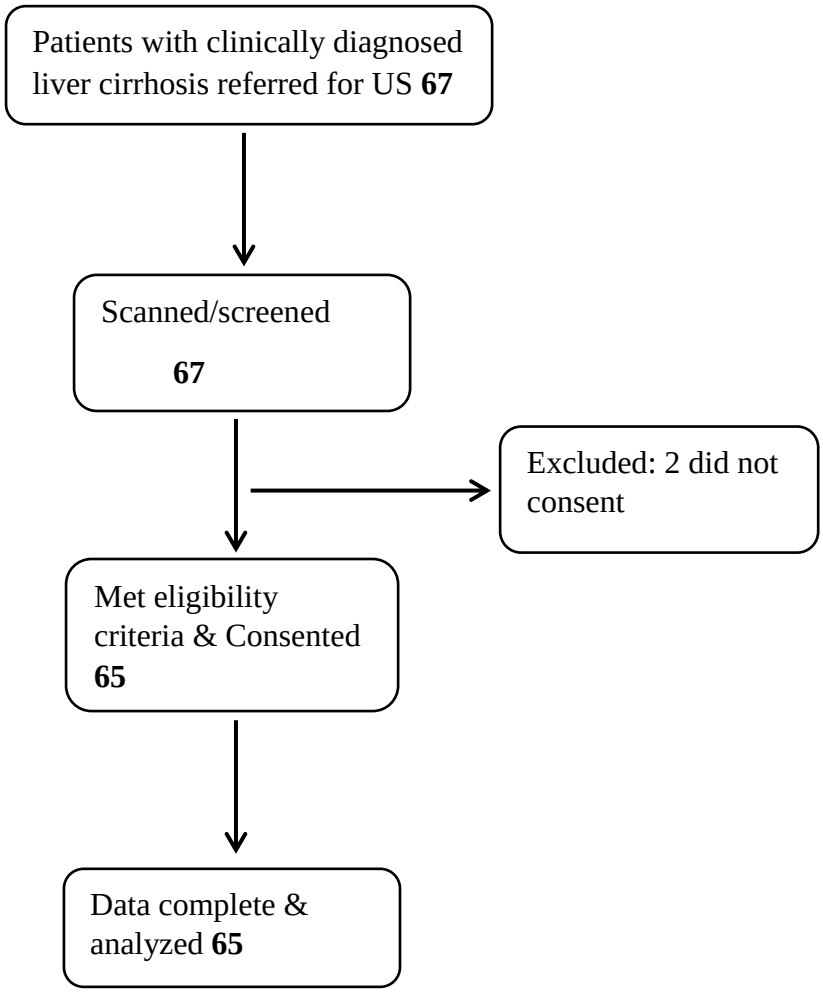
Patients who met the eligibility criteria were identified in the medical and surgical wards and clinics. Primary clinician wrote requisition for hepatobiliary ultrasound. Informed consent was sought and patients enrolled into the study. Patients were kept nil per oral atleast 6 hours prior to the examination.

A standard hepatobiliary grayscale ultrasound and Doppler ultrasound was then conducted by the principal investigator. This was done using a real time scanner with the trans-abdominal approach. Mindray M7 U/S a portable ultrasound machine with exquisite Doppler capability was used, utilizing 3.5 – 5 AMHz curvilinear probe and Doppler capability was used. The examination was done with the patient lying supine on the examination couch. The abdomen was exposed and paper towel used to protect the patient's clothes, pre-warmed coupling gel was applied to the abdomen then a standard grayscale hepatobiliary ultrasound with Doppler studies of the portal vein, hepatic veins and hepatic artery conducted with a Doppler angle of $\leq$ 60 degrees. Details of the ultrasound protocols are in the appendix. The images obtained were archived and later reviewed by the principal investigator and two consultant radiologist and a consensus of the findings recorded. Data collected was recorded in a data collection tool. Patients were given a hard copy of their results. All the information obtained was kept confidential in a secure cabinet by the principal investigator.

Standard references were used for interpretation. The following were considered as normal reference ranges in this study:

- Liver size: females (14.9 ± 1.6) , Males : (15.1 ± 1.5) (Patzak et al., 2014).
- Spleen size: <13cm (Goyal et al., 2009).
- Portal vein diameter: 11 ± 2 mm. (Phillips, n.d.).
- Portal vein velocity: ranges from 16–40 cm/sec.(McNaughton & Abu-Yousef, 2011).
- Portal vein congestive index: 0.070 ± 0.029 cm/sec and increases to 0.171 ± 0.075 cm/sec in patients with portal hypertension. (Moriyasu et al., n.d.)
- Hepatic artery resistive index : 0.55 - 0.8 (Wood et al., 2010).

3.6.1 Study Recruitment Schema



3.7 Data collection and management

3.7.1 Data collection

Data was collected between May 2019 and April 2020 using a structured questionnaire. The gathered data was de-identified and entered into an electronic database. Double data entry was done for accuracy. The database was encrypted to ensure confidentiality of the data, and the password was made available to the principal investigator alone. Back-up of the data was done to cushion against loss. Once the data had been completely converted into the electronic database, the questionnaires were kept in a safe cabinet under a lock and key, and access was allowed to the principal investigator alone. The data will be shredded after five years. Patients had a copy of their results and had autonomy over who else can be disclosed to. Serial numbers were used in order to protect patients' identity. At the end of each day data collection forms were verified for completeness and coded by assigning numerical meanings.

3.7.2 Quality control

The ultrasound was performed by the principle investigator at the MTRH ultrasound rooms. The images were reviewed by the principle investigator and at least two consultant radiologist and a consensus of the findings recorded.

3.8 Statistical data analysis and presentation

3.8.1 Data analysis

Double entry was done in MS Excel then using Statistical Package for Social Sciences (SPSS) version 23.0 software, coding and cleaning before analysis was done. Descriptive statistics were used to explore and summarize the variables; categorical variables including liver irregularities, parenchymal echogenicity, ascites, splenomegaly, hepatic vein waveform and portal vein flow pattern and presence of thrombi were summarized as proportions and percentages. Continuous variables

including age, liver size, spleen size, PV diameter, PV velocity, PV Congestive Index and HARI were analyzed using means, median, and their corresponding standard deviations and interquartile range respectively. Chi square test and Fischer's exact test were done to assess association between categorical variables predictive of portal hypertension, that is, hepatofugal flow and liver span, ascites and parenchymal echogenicity. $P < 0.05$ was considered statistically significant. Nonparametric Mann-Whitney U test was done to assess the association between continuous variables (PV velocity, diameter, CI and HARI) and categorical variables (ascites, splenomegaly and hepatofugal flow). $P< 0.05$ was considered statistically significant.

3.8.2 Data Presentation and Dissemination

The data is presented in form of charts, tables and graphs. It will be disseminated in reputable journals and conferences. The results were presented through thesis write up and oral defense to department of Radiology and Imaging, Moi University School of Medicine and to the Hospital management.

3.9 Study limitations

1. None of the patients had liver biopsy done to confirm the diagnosis of liver cirrhosis.
2. This was a hospital based study so the results could not be generalized to the general population.

3.10 Ethical considerations

- Ethical approval to carry out the study was sought and granted from the Institutional Research and Ethics Committee (IREC).
- Permission to conduct the study at MTRH was sought and granted from the CEO of Moi Teaching and Referral Hospital.

- 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 is generally safe with no potential risks.
- A consent form was used to seek informed consent from potential study participants. Informed consent to participate in the study was obtained from all adults (18 years and above) patients who met inclusion criteria.
- Interviews and examination of patients was done in a confidential room.
- All patients received medical attention as necessary regardless of their willingness/unwillingness to participate in the study. Participation in the study was on a voluntary basis, the participants were at liberty to withdraw from the study at any stage without being penalized. No incentives or inducements were used to convince patients to participate in the study.
- Patients were informed of their results and appropriate standard treatment given. Confidentiality was maintained throughout the study.
- Data collection forms used neither contained the names of the patients or their personal identification numbers. Data collection forms used were kept confidential and access limited to the principal investigator and biostatistician only. Data collection tools were kept in a locked cabinet during the study period.
- The results will be available for academic reference in the College of Health Sciences Resource Centre. It will also be availed to Radiology & Imaging department for use as necessary. The results of this research shall be published 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 Introduction

This chapter presents the findings of the study. It entails demographic information, patient history, clinical characteristics, grayscale and Doppler ultrasound findings and ultrasound features associated with portal hypertension.

4.2 Results

4.2.1 Demographic information

A total of 65 participants were studied. Of the 65 patients, 41 (63.1%) were male while 24 (36.9%) were female.

Most of the patients, 32 (49.2%) were aged between 45-54 years, 15 (23.1%) 35-44 years, 12 (18.5%) 55-64 years and 6 (9.2%) were below 35 years. (**Table 1**).

Table 1: Demographic characteristics of patients

Demographic information of patient	Frequency (n)	Percent (%)
Gender		
Male	41	63.1
Female	24	36.9
Age group		
Below 35 years	6	9.2
35-44 years	15	23.1
45-54 years	32	49.2
55- 64 years	12	18.5

The mean age of the respondents was 47 years (s.d=7.8) with a median of 48 years IQR (41.5-53.5). Distribution of the patients' age is shown in (**Figure 8)**.

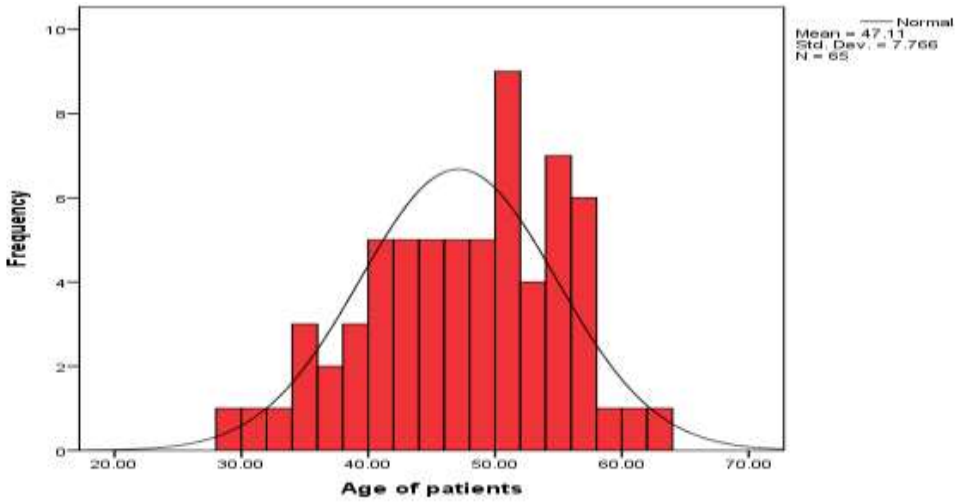


Figure 8: Distribution of the patients' age

4.2.2 Patients' history and clinical examination findings

Patient history

A total of 41 (63.1%) of the patients had yellow eyes, 51 (78.5%) had abdominal distension, and 21 (32.3%) patients reported itching while 48 (73.5%) had a history of alcohol consumption. **(Table 2).**

Table 2: History of the patient

Characteristic	Frequency (n)	Percent (%)
Presence of yellow eyes		
Yes	41	63.1
No	24	36.9
Presence of abdominal distension		
Yes	51	78.5
No	14	21.5
Presence of itching		
Yes	21	32.3
No	44	67.7
Alcohol consumption		
Yes	48	73.8
No	17	26.2

Clinical examination and laboratory findings

29 (44.6%) of the patients had pallor, and 52 (80.0%) had jaundice.

In 31 (47.7%) of the patients, the liver span was normal, 26 (40.0%) had increased liver span and 8 (12.3%) had reduced liver span.

29 (44.6%) of the patients tested positive for hepatitis infection, 24 (36.9%) tested negative while 12 (18.5%) had unknown hepatitis titres. **(Table 3).**

Table 3: Clinical and laboratory findings

Characteristic	Frequency (n)	Percent (%)
Hepatitis infection test		
Positive	29	44.6
Negative	24	36.9
Unknown titres	12	18.5
Presence of pallor		
Yes	29	44.6
No	36	55.4
Presence of jaundice		
Yes	52	80.0
No	13	20.0
Liver span characteristics		
Normal	31	47.7
Increased	26	40.0
Decreased	8	12.3

4.2.3 Objective 1: Grayscale ultrasound findings

On liver echogenicity, 40 (61.5%) had homogeneous (normal) while 25 (38.5%) were hyperechoic. **(Figure 9).**

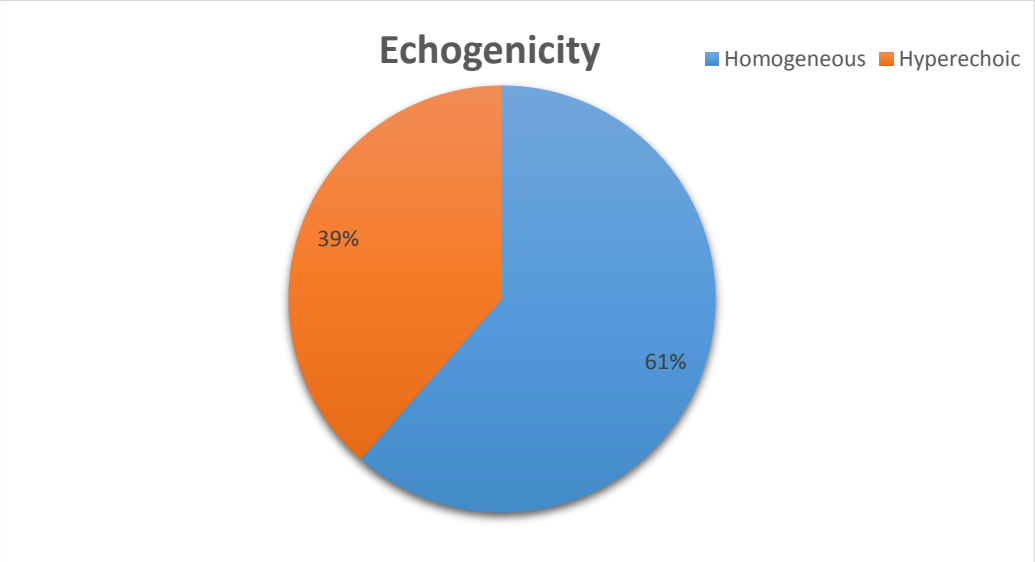


Figure 9: Echogenicity

Surface irregularities were present in 42 (64.6%) of the patients **(Figure 10).**

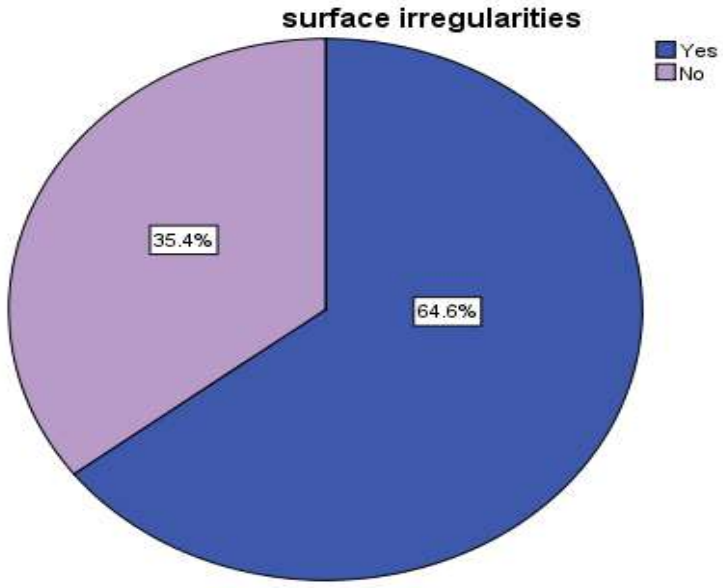


Figure 10: Presence of surface irregularities

Parenchymal nodularity was present in 14 (21.5%) of the patients, of which 3 had ill-defined echogenic liver masses **(Figure 11).**

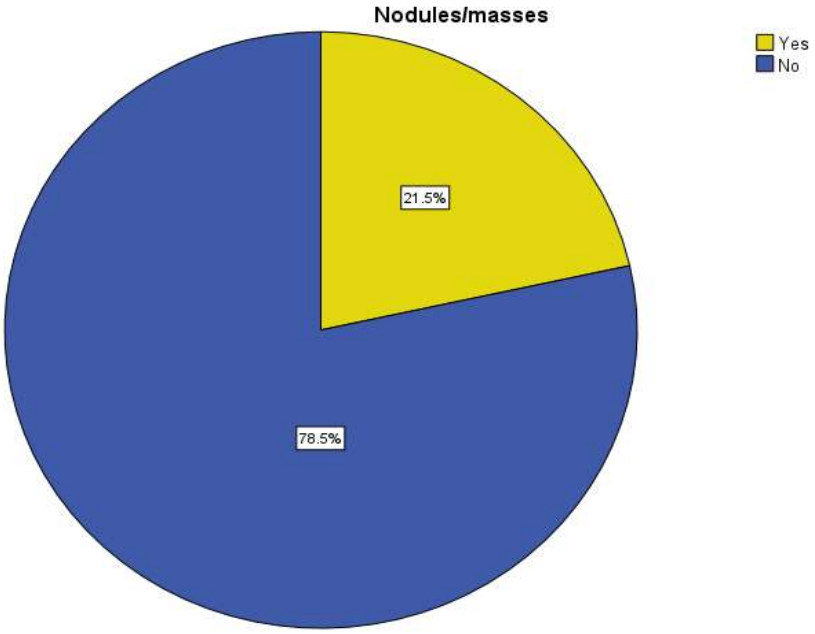


Figure 11: Presence of nodules

35 (53.8%) of the patients had ascites while 30 (46.2%) of the patients did not have ascites **(Figure 12).**

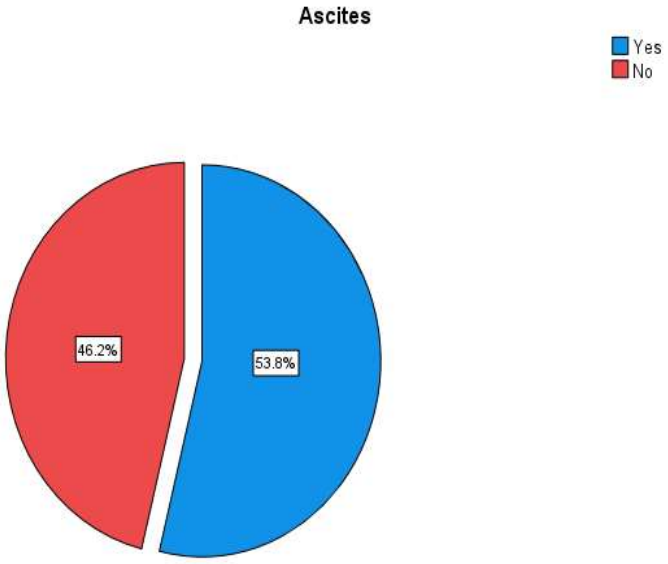


Figure 12: Presence of ascites

Splenomegaly was demonstrated in 32 (49.2%) of the patients, while 33 (50.8%) had normal spleen size. **(Figure 13).**

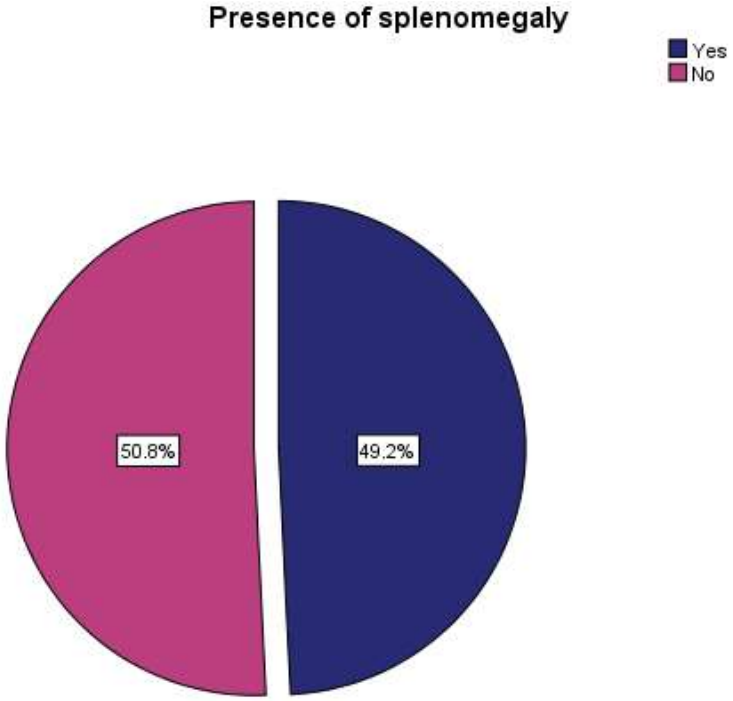


Figure 13: Presence of splenomegaly

Main portal vein diameter (MPV) was normal in 37 (56.9%) of the cases and increased in 28 (43.1%) of the cases. **(Figure 14).**

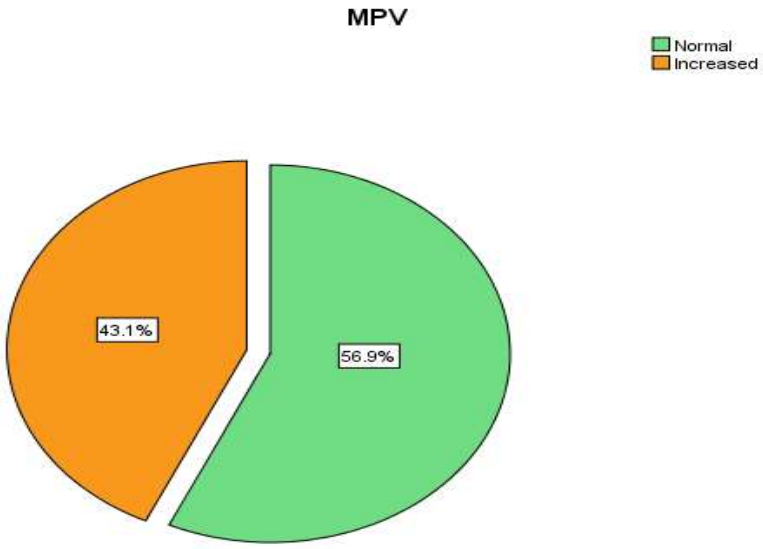


Figure 14: Main portal vein diameter

The mean liver size was 15.46 ± 1.96 cm

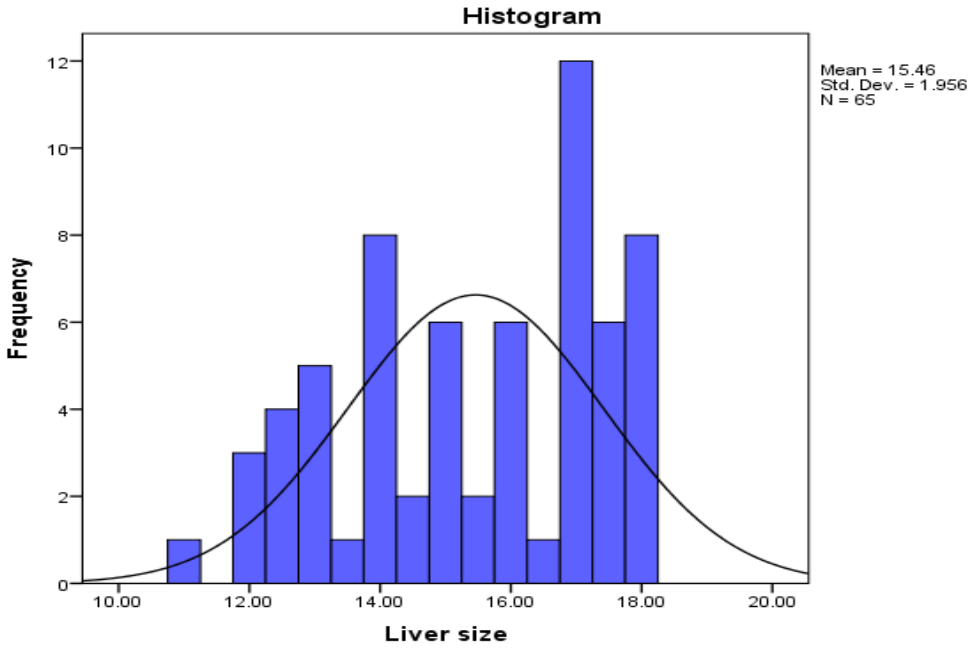


Figure 15: Distribution of liver size.

4.2.4 Objective 2: Doppler ultrasound findings of portal and hepatic vessels.

47 (72.3%) of the patients had hepatopetal PV flow while 18 (27.7%) had hepatofugal flow **(Figure 16).**

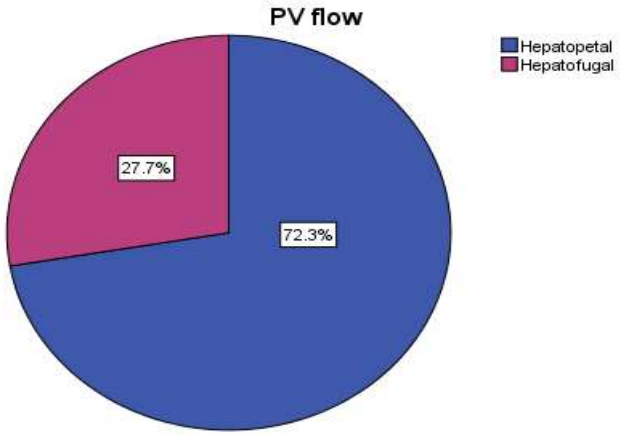


Figure 16: PV flow characteristics

On HV waveform phase, 43 (66.2%) were triphasic, 13 (20.0%) were biphasic while 9 (13.8%) were monophasic. **(Figure 15).**

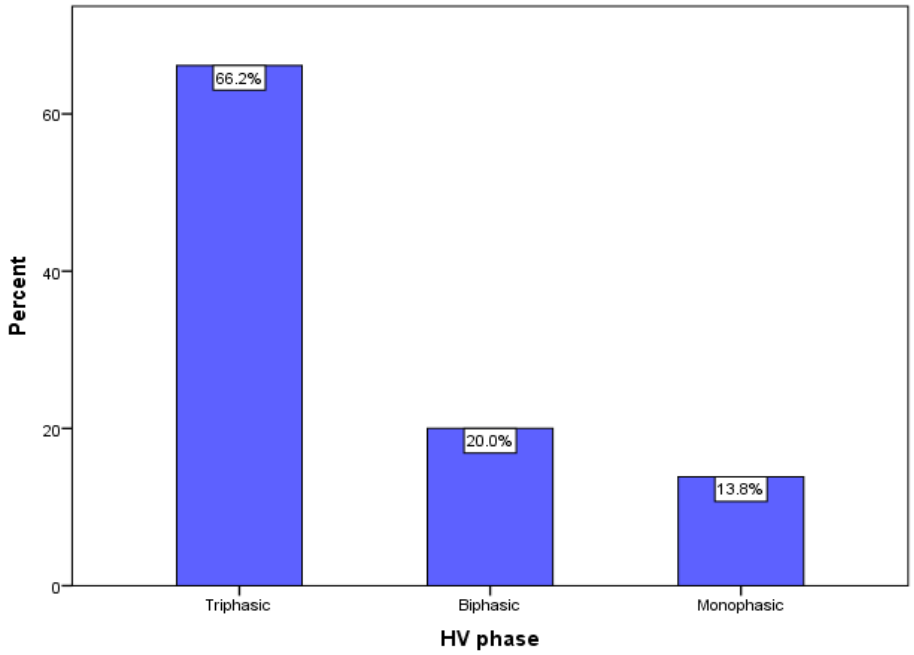


Figure 17: HV Phase characteristics

3 (4.6%) of the patients had PV thrombosis.

The mean liver size was 15.46 cm (s.d=1.96) with a median of 15.70 (IQR=17.20-12.65). The mean and median of portal vein velocity, portal vein diameter and HARI were 13.49 cm/s (s.d=1.99) with a median of 14.00(IQR=15.00- 12.00), 12.73mm, (s.d=1.62) with a median of 13.00 (IQR=14.00-11.60) and 0.76 (s.d= 0.21) with a median of 0.74 (0.91 - 0.64) respectively. The mean CI was 0.13 (s.d=0.21) with a median of 0.12 (IQR=0.09 -0.17). **(Table 4).**

Table 4: Sonography measurements

Variable	Mean ±SD	95% Cl	Median	IQR
PV velocity	13.49±1.99	13.00, 13.99	14.00	12.00-15.00
PV diameter	12.73±1.62	12.33, 13.13	13.00	11.60-14.00
HARI	0.76 ±0.21	0.71, 0.81	0.74	0.64- 0.91
CI	0.13 ±0.04	0.12, 0.14	0.12	0.09- 0.17

4.2.5 Objective 3: Ultrasound features associated with portal hypertension

There was statistically significant association between hepatofugal flow and echogenicity, hepatitis infection, alcohol consumption, splenomegaly, ascites, and liver span (P value < 0.05). **(Table 5).**

Table 5: Factors associated with hepatofugal flow pattern

Variable	Hepatofugal flow	X^2	df	p-value
Gender				
Male	12 (29.3%)	0.138	1	0.711
Female	6 (25.0%)			
Splenomegaly				
Yes	16 (50.0%)			< 0.001
No	2 (6.1%)			
Echogenicity				
Hyperechoic	15 (60.0%)	21.177	1	<0.001
Homogeneous	3 (7.5%)			
Hepatitis infection				
Unknown	1 (8.3%)			<0.001*
Positive	2 (6.9%)			
Negative	15 (62.5%)			
Alcohol consumption				
Yes	17 (35.4%)			0.026*
No	1 (5.9%)			
Ascites				
Yes	14 (40.0%)			0.025*
No	4 (13.3%)			
Liver span				
Normal	1 (3.3%)	20.711	2	<0.001*
Increased	15 (57.7%)			
Decreased	2 (22.2%)			

*Fischer's exact test

Non-parametric Mann-Whitney-U test was carried out to assess the association between median HARI, PV velocity, PV diameter, and CI among patients with hepatofugal and hepatopetal flows. The median HARI, PV diameter, and CI were significantly higher while PV velocity was lower in patients with hepatofugal compared to those hepatopetal flow (P value < 0.05). (**Table 6).**

Table 6: Association between hepatofugal flow and HARI, CI, PV diameter and PV velocity

Variable	PV flow	N	Median (IQR)	Z	U	P-value
HARI	Hepatopetal	47	0.72(0.62-0.82)	-3.60	178.0	<0.001
	Hepatofugal	18	0.90(0.74-1.00)			
PV diameter	Hepatopetal	47	12.20(11.00-13.70)	-4.58	111.0	<0.001
	Hepatofugal	18	14.10(13.56-14.23)			
CI	Hepatopetal	47	0.11(0.07-0.13)	-4.75	99.0	<0.001
	Hepatofugal	18	0.17(0.16-0.18)			
PV velocity	Hepatopetal	47	14.00(13.00-15.00)	-	64.0	<0.001
	Hepatofugal	18	12.00(11.00-12.00)	5.34		

The median HARI, PV diameter, and CI was significantly higher while PV velocity was lower in patients with splenomegaly compared to those without splenomegaly (P value < 0.05). (**Table 7).**

Table 7: Association between splenomegaly and HARI, CI, PV diameter and PV velocity

Variable	Splenomegaly	N	Median	Z	U	P-value
HARI	Yes	32	0.84	-2.28	354.5	0.023
	No	33	0.70			
PV diameter	Yes	32	13.95	-4.57	191.0	<0.001
	No	33	12.1			
CI	Yes	32	0.17	-4.43	187.5	<0.001
	No	33	0.09			
PV velocity	Yes	32	12.00	-4.04	224.5	<0.001
	No	33	15.00			

The median HARI, PV diameter, and CI were significantly higher while PV velocity was lower in patients with ascites compared to those without ascites (P value < 0.05). **(Table 8).**

Table 8: Association between ascites and HARI, CI, PV diameter and PV velocity

Variable	Ascites	N	Median	Z	U	P value
HARI	Yes	35	0.85	-2.25	354.5	0.025
	No	30	0.72			
PV diameter	Yes	35	13.70	-3.33	272.0	0.001
	No	30	12.10			
CI	Yes	35	0.16	-3.32	273.0	0.001
	No	30	0.10			
PV velocity	Yes	35	12.0	-2.59	331.0	0.010
	No	30	14.0			

SAMPLE IMAGES

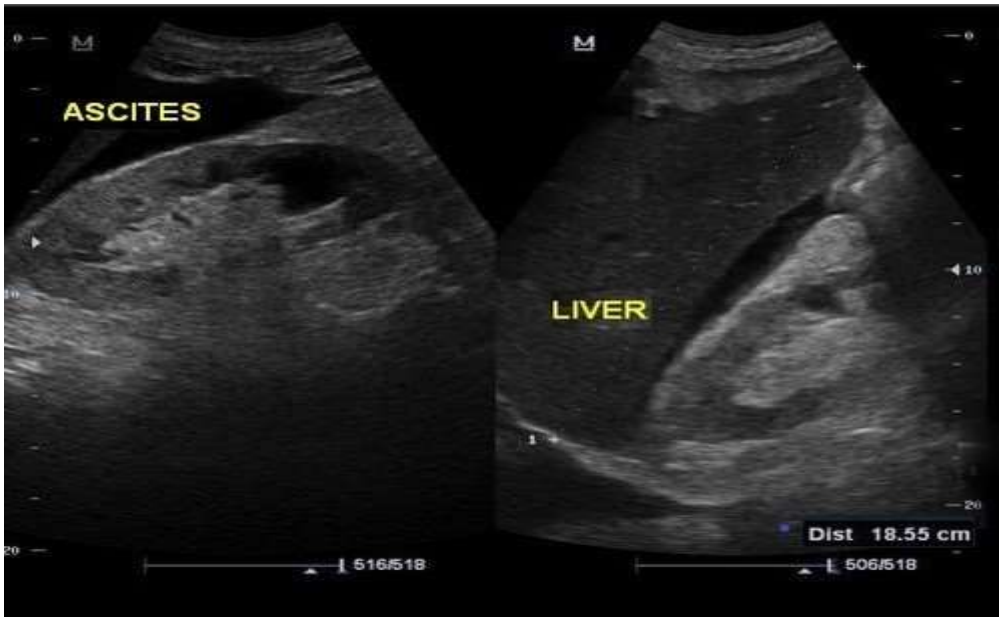


Figure 18: 47 year old male. Grayscale ultrasound images demonstrating irregular liver surface and significant ascites

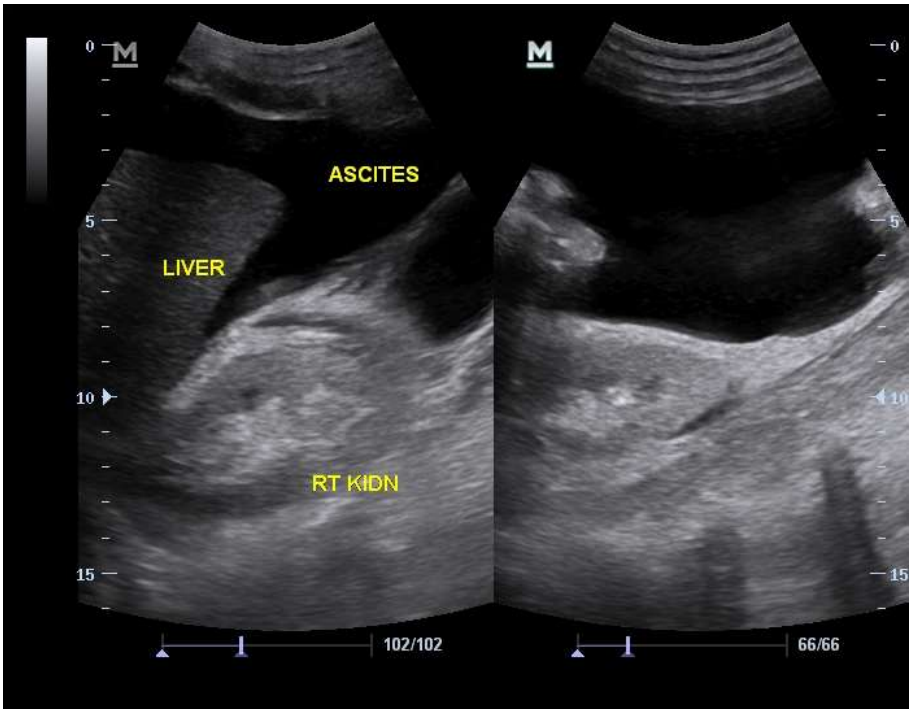


Figure 19: 42 year old female. Grayscale ultrasound images demonstrated a shrunken liver with massive ascites

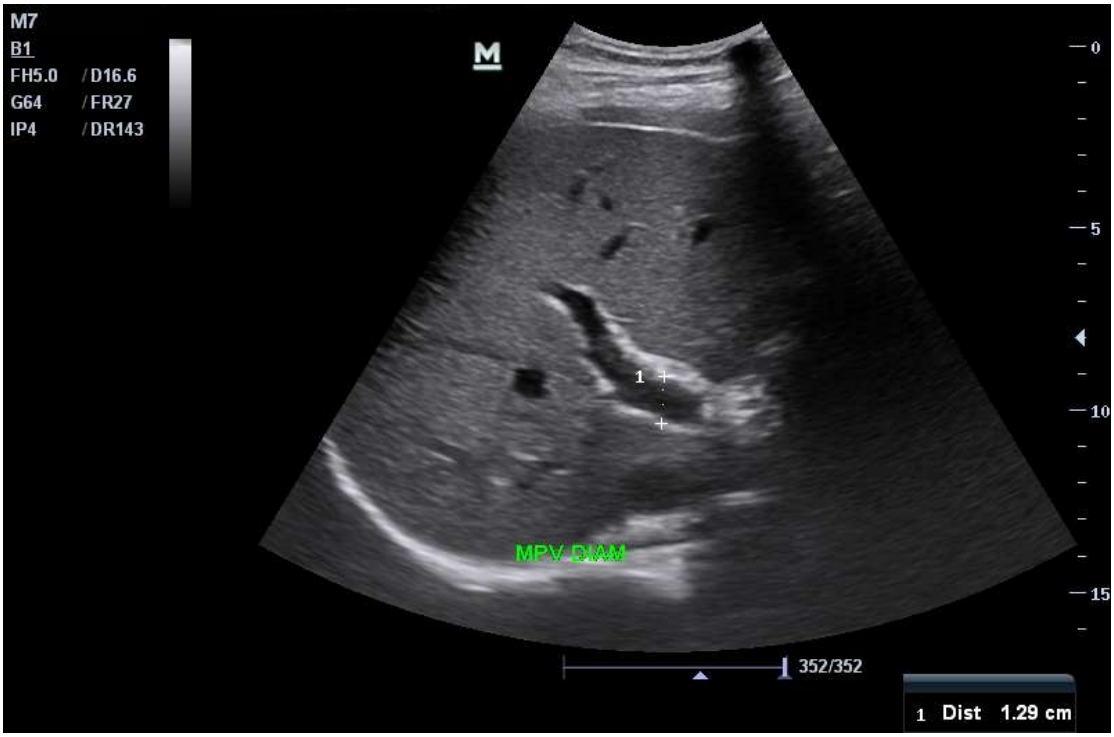


Figure 20: 36 year old. Moderate liver surface irregularities with normal main Portal vein diameter

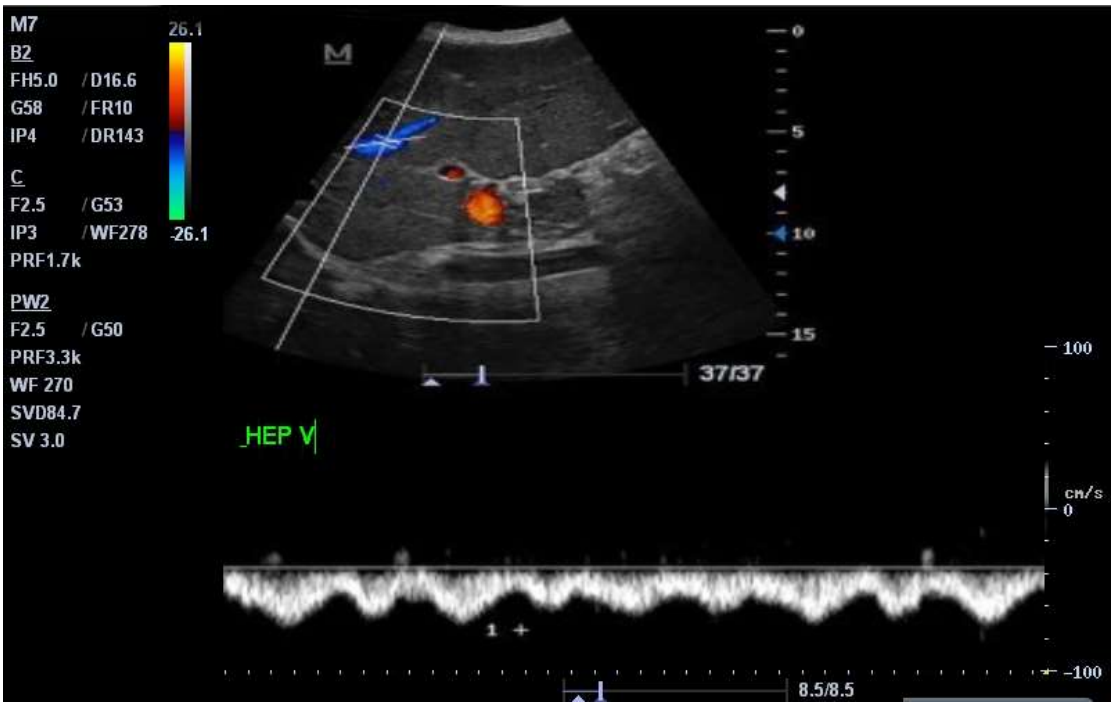


Figure 21: 31 year old male. Doppler ultrasound of the middle hepatic vein demonstrates biphasic waveform

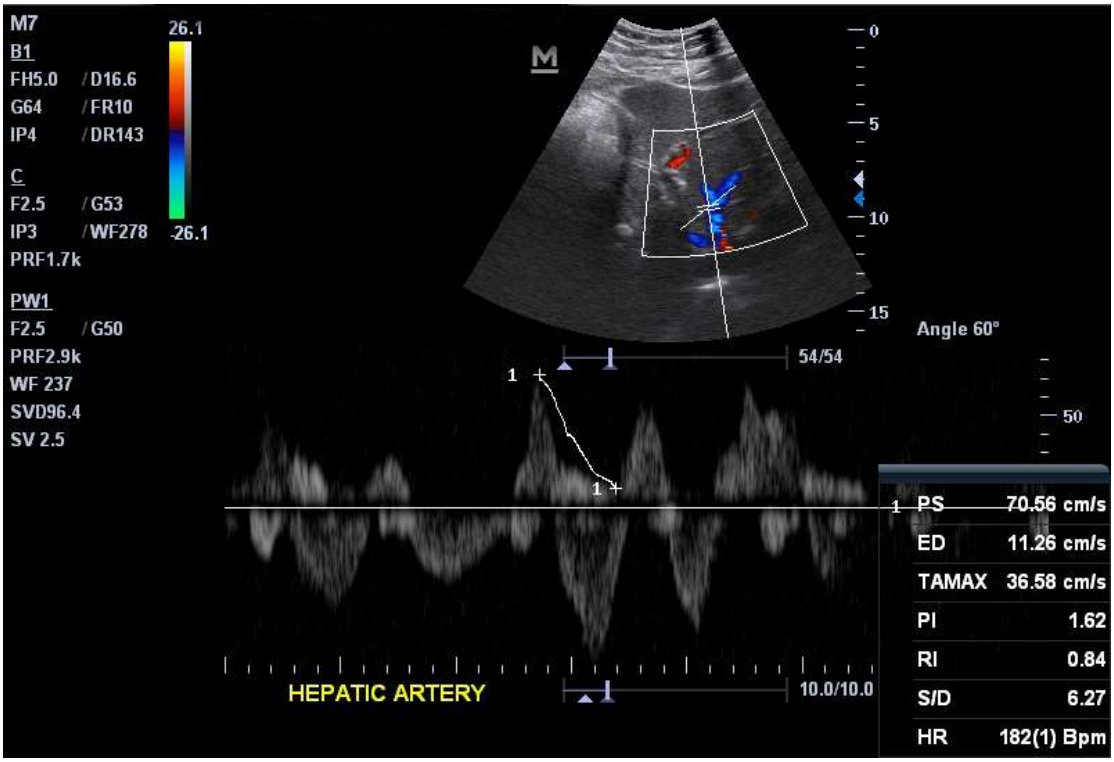


Figure 22: 53year old male. Doppler ultrasound demonstrates a slightly increased HARI of 0.84

Figure 23: 35 year old. Ultrasound demonstrates hyperechoic liver parenchyma with a normal portal vein velocity

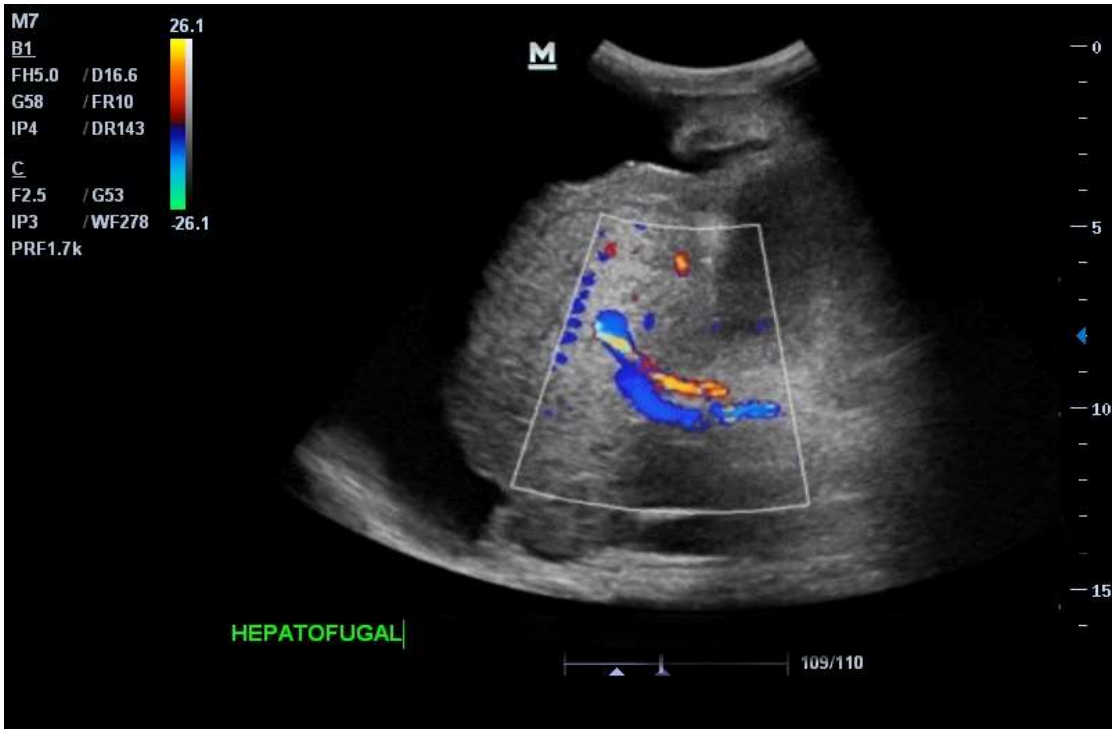


Figure 24: 51 year old male. Ultrasound demonstrates significantly shrunken liver with irregular surfaces and massive ascites. Hepatofugal portal vein flow noted

Figure 25: 42 year old male with clinically diagnosed liver cirrhosis. Doppler ultrasound demonstrates normal hepatopetal portal vein flow.

CHAPTER FIVE: DISCUSSION

5.1 Demographic characteristics

Most of the patients, 49.2%, were aged between 45-54 years, with a mean age of 47 years and median of 48 years. Similar findings were observed by Scaglione et al in USA where 41.4% of the participants aged between 45-54years with a median age of 51 years (Scaglione et al., 2015).

Majority of the patients were male at 63.1 % (41). Male have been reported to have higher prevalence of liver cirrhosis than women. Worldwide, the number of men with liver cirrhosis is twice that of women and of the 1.3 million death due to liver cirrhosis, two thirds were reported in male (Sepanlou et al., 2020).

5.1.1 Patient history and clinical characteristics

73.8% of the patients had history of alcohol consumption and 44.6% tested positive for hepatitis. Similar findings were reported in a retrospective study in Korea where most of the 20000 patient whose records were reviewed had hepatitis B virus (HBV) cirrhosis, or alcoholic cirrhosis, with that associated with alcohol consumption increasing significantly during the study period (Jang et al., 2020).

In contrast with (Scaglione et al., 2015), where alcohol consumption only accounted for 25.3% this can be attributed to the fact that he quantified excess alcohol consumption where he defined it as >2 drinks/ day in men and >1 drink/day in women within 1 year before completion of data collection.

However, Hepatitis B infection and use of alcohol have been found to be the two main risk factors and causes of liver cirrhosis (Paul Starr & Raines, 2011 & Sepanlou et al., 2020).

5.2 Ultrasound Findings

5.2.1: Objective 1: Grayscale ultrasound findings

Liver surface irregularities were present in 64.6% of the patients, this compares well with Agostino in Italy and Choong in Singapore who found surface irregularities in 54.2% and 57% of the patients respectively (Agostino Colli et al.,|N. D. & Choong et al., 2012). However, it contrasts findings by Berzigotti in Spain who found surface irregularities in only 34.8% of the patients (Berzigotti et al., 2010), this could be attributed to exclusion of patients with biopsy proven cirrhosis and the liver surface findings were stratified into: smooth, irregular and nodular.

Liver surface irregularities has been most commonly used as a sole indicator for the diagnosis of cirrhosis using conventional ultrasound (Goyal et al., 2009) however the presence of cirrhosis may be underestimated when based on a single parameter (Gaiani et al., 1997) and the use of surface irregularities is likely to result in false positives due to peritoneal based pathologies (Šimonovský, 1999).

61.5% of the patients had homogeneous parenchymal echogenicity while 38.5% were hyperechoic, these findings compares well with Aube in France who found 32.8% of the patients with hyperechoic parenchymal echogenicity (Aubé et al., 1999) while it contrasts a study by Masoni in MTRH who found only 13% of patients with hyperechoic parenchyma (Masoni,2018), this could be explained by the difference in study design, since he did an analytical crossectional study and recruited all patients that presented with jaundice hence a wide range of differential diagnosis.

Presence of irregular liver surface, straight and regular hyperechoic lines and different echogenicity of the liver parenchyma are considered positive for liver cirrhosis (Shen et al., 2006 & Goyal et al., 2009). On ultrasound, the early liver cirrhosis signs consist

of liver surface irregularities, parenchymal inhomogeneity, echogenicity, enlarged caudate lobe and splenomegaly mainly resulting from portal hypertension (Wiegand & Berg, 2013 & Shen et al., 2006).

53.8% of the patients had ascites, this compares well with Drazen in Croatia and VonHerbay in Germany who found ascites in 46.6% and 43.1% of the patients respectively (Drazen et al., 2010 & Herbay et al., 2000). However, this contrasts Berzigotti in Italy that found only 17.4% of ultrasound identified ascites (Berzigotti et al., 2011), this is attributed to his exclusion of clinically decompensated cirrhosis where ascites was used as an indicator of decompensation.

Ascites is a common finding in patients with cirrhosis and ultrasound is a sensitive technique and can detect small volumes of fluid (Goyal et al., 2009).

49.2% of the patients had splenomegaly, while 50.8% had a normal spleen size, similarly Ahmed in Egypt and Park in California demonstrated splenomegaly in 49% and 45.4% of the patients respectively (Abdelrahman et al., 2020 & Park et al., 2017), whereas O' Donohue in London found 71.5% patients with splenomegaly (O'Donohue et al., 2004), this difference could be attributed to the fact that he studied patients with biopsy proven cirrhosis and included patients with chronic liver disease secondary to HCV infection.

Liver cirrhosis with portal hypertension causes congestive splenomegaly and use of ultrasound is a non-invasive, sensitive, and specific technique for the evaluation of spleen size (Goyal et al., 2009).

5.2.2: Objectives 2: Doppler ultrasound patterns and indices of portal and hepatic vessels.

Main portal vein diameter was increased in 43.1% of the patients, with a mean diameter of 12.73 (+/- 1.62) mm this compares well with studies by Sonhaye in Togo and Berzigotti in Italy who found 52% and 55% increased portal vein caliber respectively (Sonhaye et al., 2018 & Berzigotti et al., 2011).

The mean portal vein velocity was 13.49cm/s, in comparison with Zironi in Canada, and Berzigotti in Italy who found means of 13.0 ± 3.2 cm/sec and 13.0 ± 0.7 cm/sec respectively (Zironi et al., 1992 & Berzigotti et al., 2011). Iwao et al.in Japan, found portal venous velocity to be significantly lower in patients with liver cirrhosis and esophageal varices with values of 11.0 +/- 2.4 cm/s in patients with cirrhosis and 15.9+/- 2.8 cm/s in controls (Iwao et al., 1997). However, the portal blood flow in patients with portal hypertension may be normal because of a compensatory high inflow into the portal venous system from the abdominal organs, and especially from the enlarged spleen (Jagt et al., 1999).

The normal portal vein diameter does not exceed 13mm in quiet respiration whereas in cases of portal hypertension this may exceed 13mm and with increasing portal pressures, the portal flow velocity decreases and as fluctuations disappear, flow becomes either continuous or reversed. (Goyal et al., 2009).

72.3% of the patients had a hepatopetal portal vein flow while 27.7% had hepatofugal flow, this compares well with a study by Allix in France that observed 22.5% of hepatofugal flow in patients with cirrhosis (Allix et al., 1998) but contrasts VonHerbay in Germany who found 9.17% of hepatofugal flow (Herbay et al., 2000), this is attributed to his stratification of abnormal flow into hepatofugal, bidirectional

and thrombotic flows and used Doppler angle of 50 degrees versus ≤ 60 degrees used in this study. In Germany, an overall prevalence of 8.3% of continuous hepatofugal flow in the portal vein trunk was noted though high abdominal pressures during inspiration may cause flow reversal in patients with severe right heart failure or other liver diseases (Görg et al., 2002).

In liver cirrhosis, obstruction of the hepatic venules and sinusoids by fibrosis, substantiated by arterioportal and porto-systemic shunting, eventually leading to flow reversal hence signifying more severe disease process (Gerstenmaier & Gibson, 2014).

Although divergent portal venous flow patterns have significant impact and associative value with cirrhosis liver (Iranpour et al., 2015), the portal flow may also be unaltered in cirrhotic patients due to a combination of high blood inflow from the splanchnic organs and increased resistance within the liver parenchyma(Goyal et al., 2009).

4.6% of the patients had portal vein thrombosis. Similarly, Amitrano in Italy found 8.9% of the patients with portal vein thrombois and he noted that presence of portal vein thrombosis in a patient with clinically diagnosed liver cirrhosis signifies an advanced liver disease and it is completely asymptomatic in approximately half of cases but when symptomatic, patients presents with life-threatening complications as gastrointestinal bleeding or intestinal infarction (Amitrano et al., 2004). Bolondi et al., reported a prevalence of partial or total portal vein thrombosis of 1.8% and 4.4%, respectively in patients with liver cirrhosis (L Bolondi et al., 1997). However Zocco in Italy found 16% of the patients with portal vein thrombosis, this could be attributed to his follow up assessment done after 1 year. (Zocco et al., 2009).

Mean portal vein congestive index was 0.13 ±0.04, similarly Bolognesi in Italy, Berzigotti in Italy and Annet in Belgium found means of 0.137 ±0.049, 0.17 ±0.02 and 0.15 ± 0.10 respectively (Bolognesi et al., 2011, Berzigotti et al., 2011 &Annet et al., 2003). CI is based on tendency of average PV diameter to increase as the velocity decreases and its thought to be a marker of increased portal pressures (Moriyasu et al., n.d. and Gerstenmaier & Gibson, 2014).

The mean HARI was 0.76 +/- 0.21, this compares well with Kim Choi in Korea who found mean of 0.70 +/- 0.06 and Drazen in Croatia who observed a mean of more than 0.73 (Kim et al., 2003 & Drazen et al., 2010) but contrasts Popov in Bulgaria whose mean of 0.66 +/- 0.07 was within the normal ranges (Popov et al., 2012). HARI tends to increase in liver cirrhosis and significant increase is noted in patients with associated portal vein thrombosis and resistance of hepatic arteries changes with portal pressure increase (Sacerdoti et al., 1995, Schneider et al., 1999 & Drazen et al., 2010).

However, HA resistance changes with increasing portal pressure values does not correlate with the actual severity of cirrhosis and the predictive values for chronic cirrhosis remains elusive (Paulson et al., 1997) and high values of HARI values may also be observed in chronic hepatitis and after a meal (Jagt et al., 1999 & Rumack et al., 2011).

66.2% of the patients had triphasic hepatic vein waveform, 20.0% had biphasic while 13.8% had monophasic waveform, therefore 33.8% had non-triphasic waveforms, these findings compares well with Agostino in Italy who found non-triphasic hepatic vein waveforms in 43% of the patients (Agostino Colli et al., n.d.). However, Berzigotti in Italy found abnormal HV phase in 56% (Berzigotti et al., 2011)), this

could be attributed to the fact that he did a retrospective study and recruited patients with biopsy proven cirrhosis while Sonhaye in Togo found normal HV wave form in only 36% of the patients (Sonhaye et al., 2018) since he recruited patients who had initial ultrasound done to ascertain presence of the cardinal features of cirrhosis.

Fibrosis in liver cirrhosis causes decreased hepatic parenchyma compliance resulting in decreased size of hepatic veins and demodulation, hence progressive reduction in phase oscillations (Sonhaye et al., 2018 & Bolondi, n.d.) creating biphasic or monophasic patterns (Gerstenmaier & Gibson, 2014) . Hypertrophy of the hepatocytes might also exert possible compression over the hepatic veins due to the low stretching of the hepatic capsule (Bolondi, n.d. 1991).

5.2.3: Objective 3: Ultrasound features associated with portal hypertension

Expressions of advanced liver cirrhosis and signs related to portal hypertension include splenomegaly, ascites and reversed portal flow with development of collateral varicose outflow pathways (Šimonovský, 1999 & E. C. F. Dietrich, 2010).

27.7% of the patients had hepatofugal flow with statistically significant association between hepatofugal flow and presence of ascites ($p=0.025$), increased HARI($p<0.001$) increased CI ($p<0.001$), similarly VonHerbay in Germany found significant association between hepatofugal flow and ascites ($p < 0.01$) (Herbay et al., 2000). Affif in Singapore found significant association between hepatofugal flow and increased HARI ($p=0.002$) (Afif et al., 2017).

Reversed portal vein flow has a high predictive value for presence of portal hypertension (Gerstenmaier & Gibson, 2014) and has a possible association with presence of ascites, esophageal varies and strongest association with presence of spontaneous portosystemic shunts (Görg et al., 2002 & Vizzutti et al., 2008).

49.2% of the patients had splenomegaly with statistically significant association between presence of splenomegaly and increased HARI (p=0.023), increased CI (p<0.001), increased PV diameter (p<0.001) and decreased PV velocity (p<0.001). Similar findings were reported by Bolondi in Italy who found significant association between splenomegaly and increased CI (p<0.001) (L Bolondi, 2002), Park in California who found significant association between splenomegaly and decreasing PV velocity(P=0.031)(Park et al., 2017) and Zaman in Pakistan who found association between splenomegaly and increased PV diameter(p=0.01)(Zaman et al., 2019). However, Park in California did not find significant association between splenomegaly and increased HARI (p =0.849) (Park HeeSun et al., 2017) , this could be attributed to his focus of predominantly assessing hepatic artery velocity rather than HARI.

53.8% of the patients had ascites with a statistically significant association between presence of ascites and increased HARI (p=0.025), increased CI (p=0.001) and decreased PV velocity (p=0.010). Similarly Drazen in Croatia found significant association between ascites and increased HARI (P <0.01)(Drazen et al., 2010). Martin in Germany found significant association between ascites and increased CI (p= 0.04). (Martin & Ochs, 1999) while Mittal in India and Heikal et al in Egypt found significant association between ascites and decreasing portal vein velocity (p <0.01) (Mittal et al., 2011 & Heikal I. et al, 2020)

On the contrary, Park in California did not find statistical significant association between ascites and increasing HARI or decreasing PV velocity (p=0.577, p= 0.621 respectively) (Park et al., 2017), this difference is attributed to his exclusion of clinically decompensated cirrhosis where ascites was used as an indicator of

decompensation hence a smaller proportion of patients were noted to have ascites on ultrasound evaluation.

Splenomegaly is the most common and sensitive sign of portal hypertension and acts as an independent predictor of esophageal varices and marker of clinically significant portal hypertension (CSPH) while ascites is the most common sign of clinically decompensated cirrhosis and holds significant prognostic factor (Berzigotti & Reverter, 2014). Presence of ascites and splenomegaly are associated with poor prognosis in liver cirrhosis (Abdelrahman et al., 2020).

CHAPTER SIX: CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion

1. Majority of the patients, 64.6% had liver surface irregularities, 38.5% had hyperechoic parenchymal echogenicity, 53.8% had ascites and 49.2% had splenomegaly.
2. 27.7% of the patients had hepatofugal portal vein flow, mean CI and HARI were 0.13 ± 0.04 and 0.76 ± 0.21 respectively.
3. Increasing HARI and CI were significantly associated with hepatofugal flow, ascites and splenomegaly (P value < 0.05).

6.2 Recommendations

1. There is need for ultrasonography evaluation with emphasis on Doppler studies of the portal and hepatic vasculature in patients with clinically diagnosed cirrhosis in order to inform their management locally at MTRH.
2. More research emphasis should be placed on validating and determining the strength of association of the features observed on ultrasound for the detection of cirrhosis and portal hypertension.

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APPENDICES

APPENDIX I: CONSENT FORM
English Version

Investigator: My name is Dr. Onkoba Valentine Wangecii. I am a qualified doctor, registered with the Kenya Medical Practitioners and Dentists Board. I am currently pursuing a Master's degree in Radiology and Imaging at Moi University. I would like to request you to participate in my research which is to study the use of Doppler ultrasound findings to assess complications of liver cirrhosis and aid in management of patients at Moi Teaching and Referral Hospital.

Purpose: This study will seek to describe the Doppler ultrasound findings in patients with clinically diagnosed liver cirrhosis in MTRH.

Procedure: Adult patients admitted in the medical and surgical wards, with clinically diagnosed liver cirrhosis will be recruited into the study after consent is sought. The patients will undergo hepatobiliary, both gray scale and Doppler ultrasound evaluation. Demographic data will be obtained and patients subjected to a physical examination. Data will be entered into a data collection form. Data collecting material will be kept in a locked cabinet in the office of the principal investigator 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. This study is aimed at improving management of liver cirrhosis.

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

Patient: ……. Investigator: ……. Date: ……

Swahili Version

Mpelelezi: Jina langu ni Dr. Onkoba Valentine Wangecii. Mimi ni daktari aliyehitimu na kusajiliwa na Wakaguzi wa Matibabu wa Bodi ya Kenya ya Madaktari na Madaktari wa meno. Kwa sasa ninafuatilia shahada ya Masters ya Radiolojia na Imaging katika Chuo Kikuu cha Moi. Ningependa kukuomba ushiriki katika utafiti wangu ambao ni kujifunza na kutumia matokeo ya Doppler ultrasound katika kutabiri matatizo ya cirrhosis ya ini na manufaa katika matibabu ya wagonjwa katika hospitali ya mafunzo na rufaa ya Moi.

Kusudi: Utafiti huu utajaribu kuelezea matokeo ya Doppler ultrasound kwa wagonjwa walio na cirrhosis ya ini katika hospitali ya MTRH.

Utaratibu: Wagonjwa watu wazima waliolazwa katika kata za matibabu, na wanaodhaniwa kuwa na cirrhosis ya ini watatayarishwa katika utafiti baada ya idhini kuulizwa. Wagonjwa watafanyiwa ultrasound ya kawaida na Doppler ultrasound. Data zitakusanywa kwenye fomu ya ukusanyaji data. Mkusanyiko wa data utafanywa kwa kuhojiana na kufungua maswali. Hifadhi zitakazotumika katika ukusanyaji wa data zitawekwa katika kabati iliyofungwa katika chumba cha mpelelezi mkuu kwa kipindi cha utafiti.

Faida: Hakutakuwa na manufaa ya moja kwa moja ya kushiriki katika utafiti huu. Watakaofanyiwa utafiti watakuwa na haki na kupewa ubora sawa na wale ambao hawatofanyiwa utafiti huo. Utafiti huu una lengo la kuboresha matibabu wa cirrhosis ya ini.

Hatari: Hakuna hatari 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 katika 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 ya Moi.

Weka sahihi au alama kama umekubali kushiriki katika utafiti

Mgonjwa ..... Mtafiti: ..... Tarehe: .....

APPENDIX II: DATA COLLECTION TOOL

A. SOCIO-DEMOGRAPHICS

Date: ……. Serial Number…….

Age……

Gender……Male ☐ Female ☐

County of residence.....

B. CLINICAL FINDINGS

History of:

Yellow eyes…….

Alcohol consumption ……...….. Duration of alcohol consumption……. (Years)

Abdominal distension……...

Itchiness……

Physical examination

Jaundice yes ☐ No ☐

Pallor yes ☐ No ☐

Liver span: Normal ☐ Increased ☐ Reduced ☐

Laboratory findings

Hepatitis viral infection……...

C. **ULTRASOUND EXAMINATION**

Grayscale findings

Liver Size ……..cm: Normal ☐ Reduced ☐ Enlarged ☐

Echogenicity Hypoechoic ☐ Hyperechoic ☐ Homogeneous ☐

Nodules / Masses present ☐ absent ☐

Surface irregularity present ☐ absent ☐

Ascites present ☐ absent ☐

Spleen Size ……cm

Doppler findings

Portal vein

Diameter ……mm: Normal ☐ Increased ☐ Decreased ☐

Flow to the liver: Hepatopetal ☐ Hepatofugal ☐

Velocity: Normal ☐ Increased ☐ Decreased ☐

Congestive Index……

Hepatic veins

Phase : Triphasic ☐ Biphasic ☐ Monophasic ☐

Hepatic artery Resistive Index .....

APPENDIX III: HEPATOBILIARY ULTRASOUND PROTOCOL

Patient preparation

- Inform the patient about the procedure.
- Seek consent.
- NPO at least 6hrs prior to the procedure.
- Maintain confidentiality and privacy.

Equipment required

Pre-warmed coupling gel.

3.5-5 MHz curvilinear transducer.

Positioning

-Patient wears hospital gown.

- Patient lies supine on the examination couch.

- Patient's abdomen is exposed, from the nipple levels to the iliac crest.

Imaging procedure

The examination was conducted using either of the two Minday M7 ultrasound machines in the radiology department.

Patient lies supine or right anterior oblique on the examination couch, the abdomen is exposed and paper towel used to protect patient's clothes.

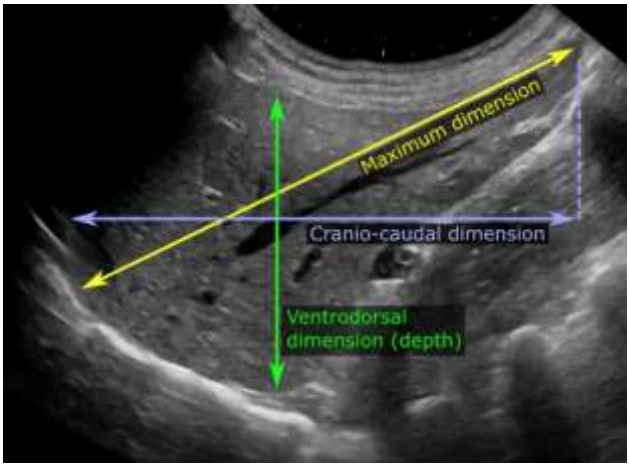
Pre-warmed coupling gel is applied to the 3.5-5 MHz curvilinear transducer and hepatobiliary ultrasound conducted.

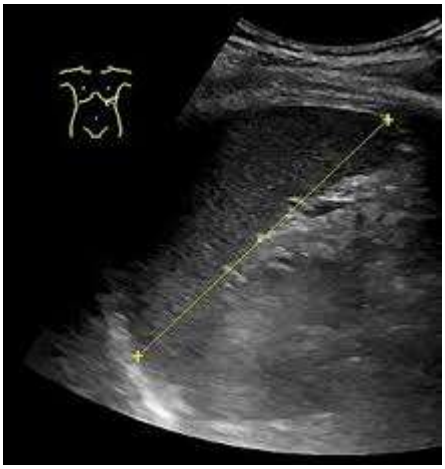
Ultrasound is done in both longitudinal and transverse planes.

Doppler ultrasonography is done (angle ≤60 degrees) and various parameters of hepatic and portal vessels assessed.

Grayscale ultrasound assessment.

- Longitudinal and transverse views are taken in the midclavicular and midline positions at the Right upper quadrant and largest craniocaudal diameter of the liver is obtained on deep inspiration.
- At the Left upper quadrant, the spleen is identified and its longest length obtained.
- Liver surface regularity, presence of nodules and echogenicity is determined.
- Presence of ascites is assessed.





Doppler ultrasound assessment.

Portal vein

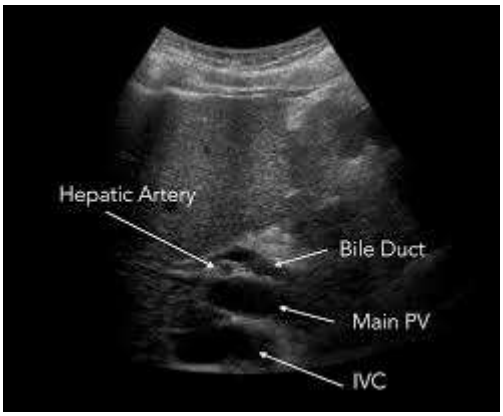
- Sonographically displayed using scans more or less perpendicular to the right lower costal margin (orientation might be achieved referring from the right shoulder to the umbilicus) preferably in variably deep inspiration.
- Using color flow imaging, it's seen as a tubular structure in the porta hepatis, branching into the right and left portal veins.
- The diameter is measured at the broadest point distal to the union of the splenic and superior mesenteric vein and portal venous velocity is determined.

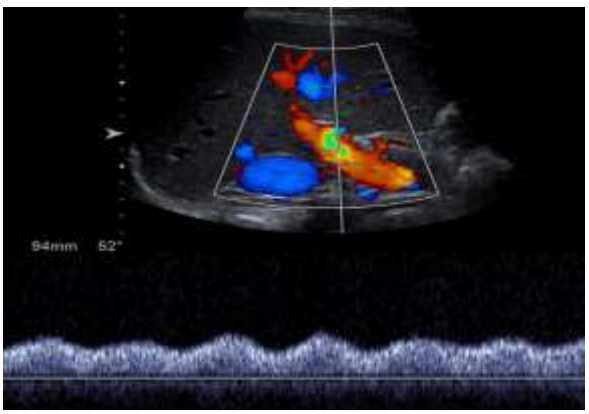
The congestion index (CI) of the portal vein is determined as follows:

Portal vein area = diameter A x diameter B x $\pi/4$

Flow velocity = 0.57 x maximum portal vein velocity (angle $\leq 60°$)

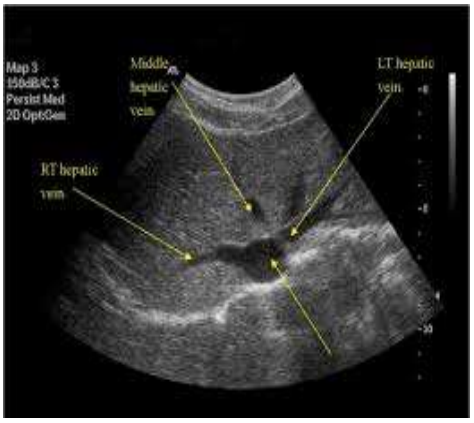
CI = vein area/flow velocity

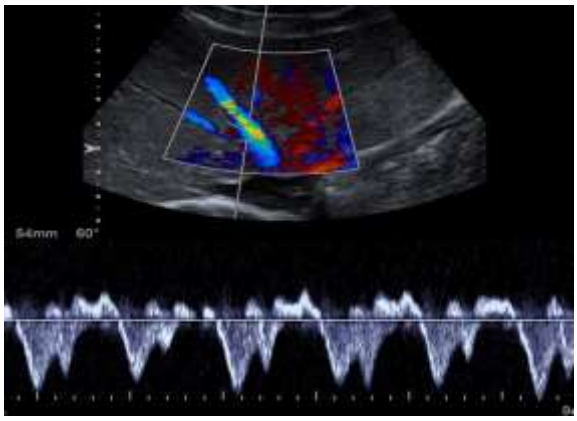




Hepatic vein

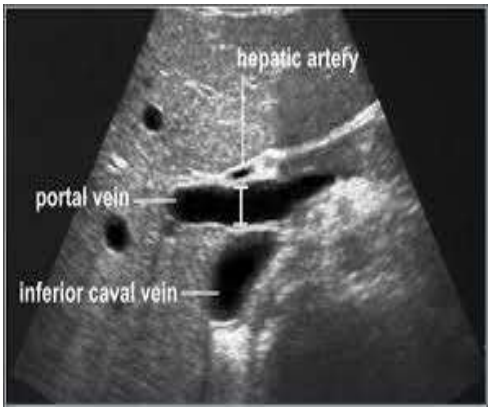
- Right lateral intercostal approach during quiet respiration.
- The middle or preferably, right hepatic vein is identified. Pulsatility within the left hepatic vein is greater due to transmitted pulsations from the heart.
- Spectral Doppler gate is placed halfway along length of the identified hepatic vein to obtain the waveforms.

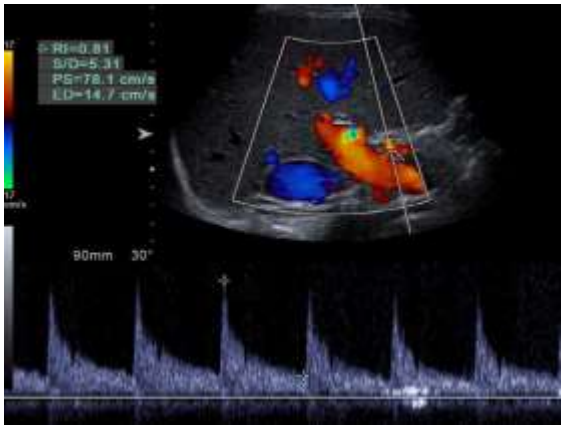




Hepatic artery

- Right oblique intercostal approach.
- Using color flow imaging, the celiac axis is located anterior to the aorta and then the arterial branch that runs to the right is followed. The hepatic artery lies anteromedial to the portal vein at the porta hepatis, 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.
- Hepatic artery RI is calculated automatically by the machine.





APPENDIX IV: IREC APPROVAL

MU/MTRH-INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE (IREC)

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

MOI UNIVERSITY
COLLEGE OF HEALTH SCIENCES
P.O. BOX 4606
ELDORET

Reference: IREC/2018/330
Approval Number: 0003326

30th May, 2019

INSTITUTIONAL RESEARCH & ETHICS COMMITTEE
30 MAY 2019
APPROVED
P. O. Box 4606 - 30100 ELDORET

Dr. Onkoba Valentine Wangecii,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

Dear Dr. Wangecii,

RE: FORMAL APPROVAL

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

"Patterns of Doppler Ultrasound Findings of Portal and Hepatic Vessels in Patients with Suspected Liver Cirrhosis at Moi Teaching and Referral Hospital".

Your proposal has been granted a Formal Approval Number: ***FAN: IREC 3326*** on 30th May, 2019. You are therefore permitted to begin your investigations.

Note that this approval is for 1 year; hence will expire on 29th May, 2020. 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 will be required to submit progress report(s) on application for continuation, at the end of the study and any other times as may be recommended by the Committee.

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. You will also be required to seek further clearance from any other regulatory body/authority that may be appropriate and applicable to the conduct of this study.

Sincerely,

DR. S. NYABERA
DEPUTY-CHAIRMAN
INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE

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

APPENDIX V: HOSPITAL APPROVAL

An ISO 9001:2015 Certified Hospital

MOI TEACHING AND REFERRAL HOSPITAL

Telephone :(+254)053-2033471/2/3/4
Mobile: 722-201277/0722-209795/0734-600461/0734-683361
Fax: 053-2061749
Email: ceo@mtrh.go.ke/directorsofficemtrh@gmail.com

Nandi Road
P.O. Box 3 – 30100
ELDORET, KENYA

Ref: ELD/MTRH/R&P/10/2/V.2/2010

4th June, 2019

Dr. Onkoba Valentine Wangecii,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

APPROVAL TO CONDUCT RESEARCH AT MTRH

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

"Patterns of Doppler Ultrasound Findings of Portal and Hepatic Vessels in Patients with Suspected Liver Cirrhosis at Moi Teaching and Referral Hospital".

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

MOI TEACHING AND REFERRAL HOSPITAL
CEO
APPROVED
04 JUN 2019
SIGN
P.O. BOX 3-30100, ELDORET

04/06/2019

DR. WILSON K. ARUASA, *MBS*
CHIEF EXECUTIVE OFFICER
MOI TEACHING AND REFERRAL HOSPITAL

cc - Senior Director, (CS)
- Director of Nursing Services (DNS)
- HOD, HRISM