ULTRASOUND IMAGING DETECTION OF HEPATOCELLULAR SUSPICIOUS LESION AMONG HIGH RISK PATIENTS ATTENDING KENYATTA NATIONAL REFERRAL HOSPITAL LIVER CLINIC

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DEPT: DIAGNOSTIC IMAGING AND RADIATION MEDICINE

UNIVERSITY OF NAIROBI

DECLARATION

I hereby declare that this proposal is my original work and it has not been presented in any other university or institution for an award of a degree or any academic credit. No section of this proposal may be reproduced in any form without prior authorization from the author or University of Nairobi.

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Supervisors Declaration

This proposal has been submitted for consideration with our approval as the University supervisors.

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DEDICATION

I would like to dedicate this work to the support system around me, to my parents, my father Mr. Mwangemi, who always encourages us never to give up in life, my mother very prayerful woman Mrs. Regina.

To my husband Mr. John for always supporting me as I work hard towards my dreams and ambitions.

To my children Ebony, Komla and Damian who are my daily strength may this inspire you in life.

To my siblings for praying and encouraging me each step of the way.

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In the name of God, the Most Merciful and the Most Beneficent. It is with the deepest senses gratitude of the almighty that gives strength and ability to complete this thesis successfully. First of all, I would like to express my sincere appreciation to my supervisors, Dr Mutala Musila Timothy, Dr Onyango Stephen Oyoo for their valuable and constructive suggestions during the planning and development of this research and to Dr Gladys Mwango the Chairperson Department of Diagnostic Imaging and Radiation Medicine University of Nairobi, and Dr Mamai Amo Head of Department Radiology, Kenyatta National Hospital for their continued support and advice

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My deep thanks also goes to others who have provided assistance at various occasions direct or indirectly in the completion of my dissertation. Last, but certainly not least, very special thanks goes to my statistician Wycliffe Ayieko for his advice, he has been a great help in the data analysis and to my research assistant Miss Veronicah Wanjiku Kung'u.

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LIST OF ABBREVIATIONS

AFP – Alpha Fetoprotein

HCC- Hepatocellular Carcinoma

DCP- Descarboxy Prothrombin

HBV- Hepatitis B virus

HCV- Hepatitis C virus

KNH- Kenyatta National Hospital

CT- Computed Tomography

MRI- Magnetic Resonance Imaging

KNH-UON ERC – Ethics Research Committee

Ppb	Parts per billion
SPSS	Statistical package for social sciences
WHO	World Health Organization
KEBS	Kenya Bureau Standard
PS	Performance status
KEMRI	Kenya Medical Research Institute
EASL	European Association for the study of the liver
AASLD	American Association for the Study of Liver Diseases
NASH	Nonalcoholic steatohepatitis

AFM1	Aflatoxins M1
OR	Odds ratio
LI-RADS	Liver Reporting and Data System

ABSTRACT

Introduction

Hepatocellular carcinoma is a primary cancer of the liver. It's the fifth most common cancer in men and the seventh most common in women worldwide(1). It's amongst the leading cause of high rates of cancer related mortality in the world and in the country. Its main risk factors in Sub Sahara Africa is infectious cause from Hepatitis B virus and Hepatitis C virus, followed by non-infectious causes such as chronic alcohol intake and aflatoxins. The latter is fungal contamination of stored food. Screening is recommended for early detection of HCC and management. However, different regions have varying protocols on tools to be used for screening. MRI has a role in particularly detection and characterization of small tumours 1-2cm, with a sensitivity of up to 84% (2). The aim of the study was to determine the prevalence of hepatocellular suspicious lesions on ultrasonic screening in high-risk patients and assign the positive ultrasound findings a LI-RADS category on multiphasic CT examination in the patients attending liver clinic at KNH.

Methodology

A Cross-sectional study was carried out at the liver clinic in Kenyatta National Hospital. Ultrasound screening was done to all HCC high risk patients. Any Ultrasound suspicious lesion for HCC was further studied using Tri-phasic Computed tomography (CT) machine.

The study included a total of 106 participants.

The data was analyzed using statistical package for social scientists (SPSS) computer software package and the results presented in the form of tables, charts and graphs.

Results

One hundred and six patients underwent Trans abdominal ultrasound and multiphasic CT scan. All these patients were included in the statistical analysis. The mean age of the patients was 39.4 (SD 12.8) years, while the median age was 37.5 (IQR 29.0 – 46.0) years. There were 65 (61.3%) male patients, while 41 (38.7%) who were female. Majority of the patients were from Nairobi (80, 75.5%).

The laboratory results indicated that 75 (70.8%) of the patients had HBsAg and 4 (3.8%) HCsAg positive results. On the history of alcohol intake, 43 (40.6%) of them had a history of alcohol intake.

The distribution of the ultrasound diagnosis of the patients revealed that of the 106 patients, 25 (23.6%) had liver cirrhosis, 10 (9.4%) had hepatitis, 6 (5.6%) had liver lesions and 2 (1.9%) were definite HCC and 2.8% of these were malignant suspicious of HCC, and the rest of the patients (61, 57.5%) had normal findings.

The six patients underwent tri-phasic CT scanning and each lesion was given a LI-RADS (LR) classification. Two patient LR 5 (definite HCC), one patients LR 4 (probably HCC), two with LR-M, and one patient LR 3 (indeterminate).

Conclusions

Our study demonstrated a prevalence of suspicious lesions of 5.66%. Multiphasic CT was capable to correctly characterize all of them with 1.9% showing features of definite HCC and 2.8% were malignant suspicious of HCC.

It also demonstrated that a well-organized radiological diagnostic pathway can be achieved in HCC screening even in a lower middle income country like Kenya.

Recommendations for Further Research

The study recommends that for the high risk patients a screening program should be established in Kenya.

1. CHAPTER ONE

1.1. INTRODUCTION

Cancer incidence and mortality are rapidly growing worldwide (3). The cancer incidence was 18.1 million in 2018 with 9.6 million of these leading to death. In the same year Bray et al., (2018) found global liver cancer mortality to be at 8.2%. This made liver cancer to be the third most common cause of cancer mortality (5). American cancer society showed an upward trend of 2.5% deaths related to liver cancer per year. Currently in Kenya, there is no cancer population based data but Ferlay et al., (2015) estimated yearly liver incidence and mortality to be 37,000 and 28,000 respectively. Other findings have found liver cancer to be more common in men than women (7).

Screening is the preclinical stage of looking for cancer (8). WHO (2) recommends a screening tool that is affordable and available with no risks to patient. Commonly used screening tools for Hepatocellular Cancer (HCC) are Ultrasound, Tumor makers α-fetoprotein (AFP), Descarboxy Prothrombin (DCP), CT scan and MRI (9–11). DCP is not a useful screening tool but a diagnostic tool because elevation signifies vascular invasion meaning there is advanced stage HCC (10). Ultrasound, however, is a useful tool compared to AFP. Ungtrakul et al., (2016) used ultrasound and AFP to screen for HCC where the ultrasound picked 16/17 lesions with a 94% sensitivity and 82% specificity while AFP picked 7/17 lesions with a sensitivity of 41% and specificity of 98%. Apart from AFP having low sensitivity to HCC lesions, it has also been found to be susceptible to effects of pregnancy, hepatitis, cirrhosis and high alanine aminotransferase (8). Worland, Harrison, Delmenico, & Dowling, (2018) showed that AFP screening is likely to give underreported results because it picked 53% of HCC lesions while the ultrasound picked 85% in the same population. However, the incongruent screening results could

be because of the HCC risk factor under study. This is because both tools were able to pick up 25% HCC lesions among people with non-viral cirrhosis (13).

For extent of tumor invasion and characterization of the lesion CT and MRI are used (11). CT uses radiation therefore has a risk of developing cancer, while MRI is expensive and inaccessible to many people (10).

Hepatocellular carcinoma is the abnormal overgrowth of liver cells in the background of chronic liver disease. With more than 80% of the cases being diagnosed in Sub-Saharan Africa and East Asia (14). It is 85% - 90% more common than other primary liver cancers (15) like intrahepatic cholangiocarcinoma, hepatic angiosarcoma, primary lymphoma and hepatoblastoma seen in children.

The major risk factor is chronic hepatitis B virus (HBV) infection at 60% transmitted through body fluids (16). At 51% in the US (17), 85% of patients with HCC had positive HBsAg, globally 55% and in endemic area 89%. (18). Other major risk factors include HCV, hepatocarcinogen aflatoxin, alcoholic liver disease which cause HCC by scar tissue and genotoxic (19) and nonalcoholic fatty liver disease- nonalcoholic steatohepatitis (NASH) (5). Life style diseases like obesity and diabetes mellitus cause NASH. The 2 are leading cause of HCC in US (5). In US 32% cases of HCC were associated with chronic consumption of alcohol more than 80g/day for 10 years (20) and 45% in Italy with more than 60g/day (21). In Europe 60–80% of liver-related mortality (22).

Aflatoxin is a mycotoxin produced by Aspergillus flavus fungus that contaminates stored foods such as rice, peanuts, common in Eastern Kenya.

Ultrasound Screening for HCC in high risk patients is recommended every six months (23). Marrero et al average tumor doubling for HCC is 117days and 3–5 months (24) (23).

Despite Kenya being endemic area there is no national policy on ultrasound protocols for screening of high risk patients. What is being used is European / American Association for Study of Liver Disease (EASL/AASL) protocols.

HCC is among the top three disease in the country with high mortality rate, affecting both sexes. Thus there is need to appraise our own Kenyan ultrasound protocols for screening high risk patients. Our study was to determine through ultrasound screening the prevalence of hepatocellular suspicious lesions in high-risk patients attending liver clinic at KNH. Also assign the positive of ultrasound findings a LI-RADS category on multiphasic CT examination and determine the distribution of the clinical risk factors in patients attending Kenyatta National Hospital.

1.2. LITERATURE REVIEW

Hepatocellular carcinoma (HCC) also called hepatoma, is the most common primary liver malignancy, accounting for 85% to 90% of all primary liver cancers. (14). It starts in the hepatocellular cells (24). The annual incidence of liver cancer has been increasing yearly, in 2011, the incidence of HCC was 1.5% per year (25). While in 2019 the incidences heightened by 3-4% (24).

Worldwide mortality related to cancer is ranked third, lung being first and stomach cancer second (4,26). Liver cancer is the most common in low-income and middle-income countries than in developed countries (24). According to Sherman, (2010) global incidence is between 250,000 and 1,000,000 per year with a male-female ratio of about 5:1, which puts it at sixth commonest cancer globally, (26). In 2006 it was found out that HCC was the fifth common carcinoma in men and seventh among women (6) while in 2010 statistics according to Ferenci et al., (2010) found it was the eighth most common in women. In 2019 the position of liver cancer related deaths for both men and women changed (Matsushita & Takaki, (2019),to second highest in men and the sixth highest in women.

The predisposing risk factors for HCC varies with region, and includes chronic hepatitis B and C virus, chronic alcohol intake, diabetes mellitus, obesity, autoimmune hepatitis, (27) and dietary exposure to mycotoxin produced by Aspergillus flavus aflatoxins (28). Obesity and diabetes mellitus have been associated with twice increased risk of HCC (4) . In some parts of Asia and Sub- Saharan Africa infective disease (from Hepatitis B and C virus) cause was top most risk factor of HCC (15). According to Jemal et al., (2011) 60% of the liver cancer was due to HBV infection. Thailand, had a HBV incidence of 12000 per year (11). HCV annual

incidence of HCC in cirrhosis was between 1.5%-4.5% and in both alcoholic and non-alcoholic steatohepatitis (NASH) cirrhosis was 2.6%(27)

Screening is the utilization of a tool or test to identify a disease in a high risk population with no signs or symptoms of that disease. The main objective being to detect the disease the earliest possible, when intervention are more efficacious, with the final aim of decreasing disease-specific deaths (29).

Observation intervals for HCC are based around tumor doubling time which range from 1 to 19 months with an average of four to six months (30). Most study protocols run screening six monthly (30).

Screening tools used are Ultrasonography, Serological tests-Tumor makers α-fetoprotein (AFP), Descarboxy Prothrombin (DCP), CT scan and MRI (8–10,26).

Management of HCC purely depends on liver function test using Child–Pugh classification (26).

1.2.1 ALCOHOL AND HCC

A study showed Alcohol-attributable liver cancer mortality as 46.5% for women and 48.5% men (31). In Europe, in 2010, 43500 deaths were caused by alcoholic cirrhosis, which is a number one risk factor of HCC (32).

In United States and northern Europe, alcohol related cirrhosis was the main risk factor making up to 32% to 45% of HCC. The mechanism of developing HCC is genotoxic which is direct effect to the liver cells or indirectly through cirrhosis development (18). Alcohol damages the liver through endo- toxins, oxidative stress, and inflammation (18).

A study done In Italy in 2014 showed a relationship between alcohol consumption of more than 80g/day with chronic Hepatitis B and C virus, and diabetes. They found out that alcohol with either the virus had an OR (Odd Ratio) of 53.9, independently alcohol had an OR of 2.4 and the virus 19.1 (18). Alcohol with either types of Diabetes had an OR of 9.9 while diabetes alone had an OR of 2.4 (18). The OR of developing HCC was high when dealing with multiple risk factor in the same patient.

The relationship between alcohol intake and development of cirrhosis and HCC is a linear dose–response relationship, the risk increased with increase in alcohol intake. A cohort study done in northern Italian communities showed that, the risk of cirrhosis was high with an alcohol consumption of 30–50 g/day and for HCC was with alcohol intake of more than 60–100 g/day. There was a risk of developing cirrhosis with an average daily intake of 60-80g/day of alcohol, with women progression being rapid than men (24). A case-control study was done in Henan, China by Zhang et al., (1998) showed a 3–4-fold risk increase of development of hepatocellular carcinoma (HCC) among heavy alcohol drinkers.

$$\text{Grams of alcohol} = \frac{\text{Volume of drink} \times \%\ \text{ABV (Alcohol by volume)}}{1000}$$

According to International Alliance for Responsible Drinking (IARD) it recommends that a woman should drink half what a man takes. In Namibia men up to 20g/day and women up to 10mg/day (33).

There is an association of alcohol consumption with development of HCC. The higher the daily consumption the higher the risk of developing H CC. This relation will be studied in this research.

1.2.2 HEPATITIS B VIRUS

In Europe, North America, and Japan, HCC is common in patients with HBV induced cirrhosis. The probability increasing with increase in HBV viral load and in elderly men. In China and Africa, 75% of HCC are due to hepatitis B virus exposure. In south of Sahara , majority of the patients with HCC were younger because of early transmission through vertical transmission of the virus (26).

In France there was a different finding 25% of patients who had HCC had either the least or no cirrhosis. But there was also a 5–15-fold increased probability for HCC amongst chronic HBV carriers compared with the general population, (30). Kenya being in sub-Sahara Africa the risk of HBV induced HCC is high.

1.2.3 HEPATITS C VIRUS

In Japan, the United States, Latin America, and Europe, the significant cause of HCC is Hepatitis C virus, with an incidence of 2–8% per year. In Japan, they had 75–80% deaths related to HCC secondary to HCV infection. The risk factors to HCV were blood transfusions, intravenous drug use, and the recycling of syringes and needles (26).

In 2005 a study in USA showed that annually 1-4% of HCV induced cirrhosis complicated to HCC (30). In general population chronic infection from HCV had a 24 fold probability of developing HCC, Genotype 1 b having the greatest risk (30). HCV lead to liver cirrhosis which is a risk factor of HCC development.

According to the above findings HBV and HCV increase chances of contracting HCC with incidence varying from one region to another. Kenya being endemic country for HBV and HCV there is need for screening of HCC in Kenyan high risk population.

1.2.4 AFLATOXINS

Aflatoxin is a poisonous substance produced by fungi Aspergillus flavus, common in Sub-Sahara African- tropical developing countries like Kenya. Amid staple foods affected are cereals as rice, maize and wheat, cassava, groundnuts, milk and milk products (34). In human significant subjection to Aflatoxins is from groundnuts and maize (35). Almost 82% of the HCC related to dietary exposure to aflatoxins occur in Asia and sub-Saharan Africa (36).

The common subtypes of naturally occurring Aflatoxins are AFB1 associated with cancer, AFB2, AFG1, and AFG2. AFM1 and AFM2 are metabolites of AFB1 and AFB2 respectively found in animal urine and milk fed on AFB1 poisoned feeds (37).

Aflatoxins pollution can occur anywhere along the production chain from collection in the field, during storage, conveyance and processing.

A retrospective study done at Moi Teaching and Referral Hospital in January 2010 to December 2012 showed 19.73% prevalence of aflatoxin induced HCC from peanuts consumption for patients from Busia and Kisii Central districts (38).

A study done in 2014 in Kenya Makueni County, out of 597 cereal samples collected, 83.4% had aflatoxins, which is a risk factor of developing HCC. Makindu Division had a highest exposures ($p<0.05$) levels of aflatoxin (OR=1.4) followed by Kaiti division then Wote Divisions (39).

A study done in Nairobi county in Kasarani sub-county from smallholder dairy farms showed that cow milk was contaminated with AFM1 with values exceeding 50ng/kg (40).

Another recent study published in 2017 on human breast milk in Makueni and Nandi counties showed presences of Aflatoxins M1 at 86.7% and 56.7% respectively. Where in

Makueni, according to European Union 10.2% were above the ceiling of 25ng/kg (ppt) of AFM1(41). In the same study it showed that majority of homesteads relied on consumption of home grown maize and sorghum which was also contaminated with Aflatoxins. Maize being 68.3% in Nandi and 80.4% in Makueni, with 24.5% of the samples consisting aflatoxins level of more than 10 ppb.

A different study done in Makueni county –Makindu, Wote and Kaiti sub counties showed A high portion of 81.7% of the maize samples were aflatoxin positive with 27% of them with values varying from 10ppb to 288.7ppb above the normal which is expected (39).

A study done in Nairobi county on level of aflatoxins on processed and non-processed maize, rice and groundnuts, majority of the showed high levels of aflatoxins above the expected extreme limit of 20ppb as per WHO/FDA/KEBS standards. The highest level of aflatoxins was picked in groundnuts. There was low mean aflatoxins level in non-processed food compared to processed for example processed maize Levels of aflatoxin was (101.20 ± 21.30 ppb) were considerably higher than that in the non-processed maize (49.70 ± 14.70 ppb) same applied to rice and groundnuts (42).

Aflatoxins is still a public health problem in Kenya especially with its role in HCC development. Various regions in Kenya have a high exposure to aflatoxins which leads to increase incidence of HCC. It is therefore important to have HCC screening done for the Kenyan population

1.3 SCREENING

Criteria for hepatocellular carcinoma screening, ultrasound screening interlude of 6–12 months is recommended for the high-risk patient, Hepatitis B carriers, Hepatitis C, all patients

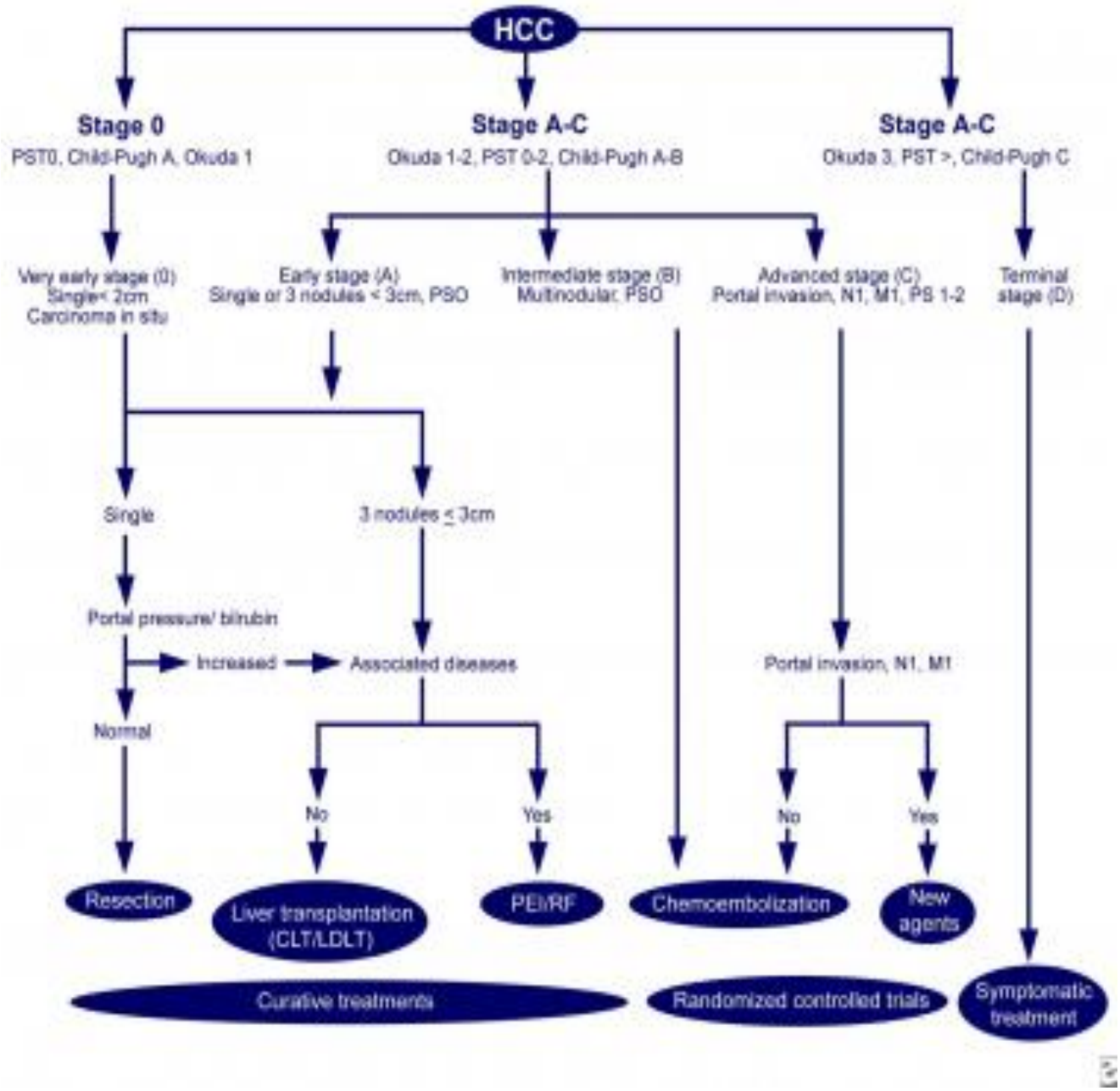
with cirrhosis irrespective of cause, positive family history of HCC, Nonalcoholic steatohepatitis (26). Age is also considered as a risk factors in patients such as young African men at age 20, middle aged Asian men and women of Asian/African decent aged more than 50years (26).

The following are different tools used for screening:

1.3.1 ULTRASOUND

Ultrasound screening interlude of 6–12 months is advised, in Liver cirrhosis, the screening should be after four to six months, because of the multiplication time of the tumor, (26). Results of ultrasound as a screening tool are better compared to tumor makers but has a major limitation of being operator-dependent (different ultrasound operator might get different results from the same patient), experience of the operator, habitus of the patient like being and the type of machine used because of different protocols used. Improvement of the sensitivity was seen when both Ultrasonography and AFP , but not suitable, due to costs implications and false-positive rates (26).

The Barcelona Clinic Liver Cancer (BCLC) staging of HCC (25).



Ultrasound (US) imaging in United States is being used to detect small hypoechoic hepatic tumors less than 3 cm, with or without positive AFP results (30).

There are variations in sonographic appearance of HCC lesion due to the existence of fat, calcium, and cell death like larger HCC lesions are bright with an infiltrative or mosaic pattern encompassed by a thin dark fibrous capsule (30).

Bialecki & Di Bisceglie, (2005), showed that combination of both Ultrasound and AFP had a high positive predictive value (PPV) at 94%. He also demonstrated that Computed Tomography (CT) scan had a higher sensitivity for diagnosing HCC at 88% than Ultrasound and AFP but it's less available and expensive. However, in a recent survey in the United States 25% of hepatologists use AFP on their high-risk patients. Few data is documented as regards magnetic resonance imaging (MRI) as a screen apparatus for HCC and it's also less available and expensive (30). The utility of Ultrasound for screening is highly sensitive in picking up the lesions. In this study we will use Ultrasound as a screening tool because of the aforementioned and also because of its availability and affordability compared to CT scan and MRI imaging. Ultrasound is safe to use because it has no harmful radiations though it is operator dependent.

Ultrasound elastography this is a new technology which is non-invasive assessment of thickening and scarring of liver parenchyma. It is useful in viral hepatitis grading of liver fibrosis. Most common used is shear wave elastography (SWE)(43). It is replacing the invasive procedure of liver biopsy in determining fibrosis and is useful in forecasting hepatocellular progression(44). (45) Used elastography for follow up of fibrosis patient and evaluation of patients with chronic liver disease.

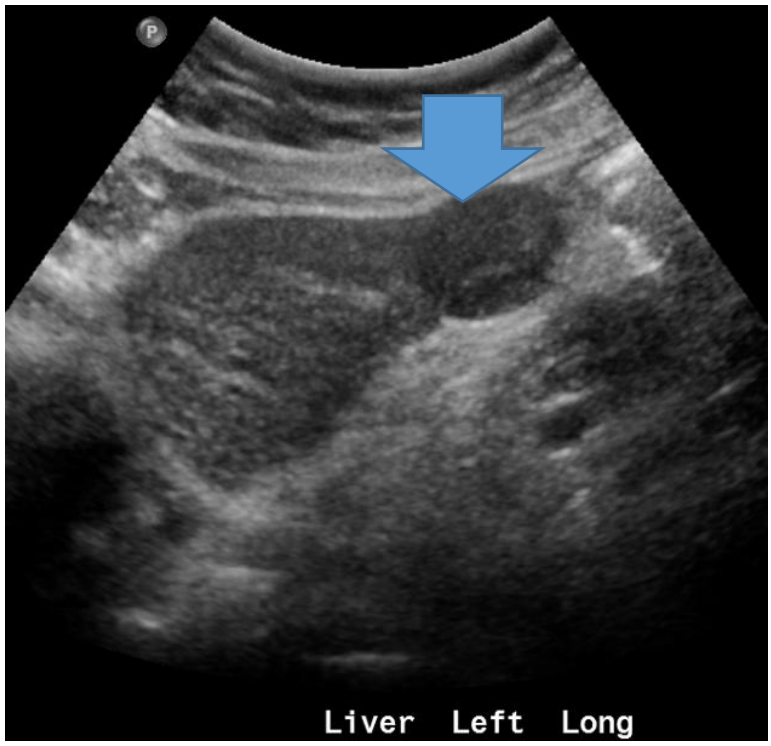


Fig 1: Left liver lobe showing a hypoechoic solid mass (arrow)

Image from https://pubs.rsna.org/author/Choi%2C+Jin-Young

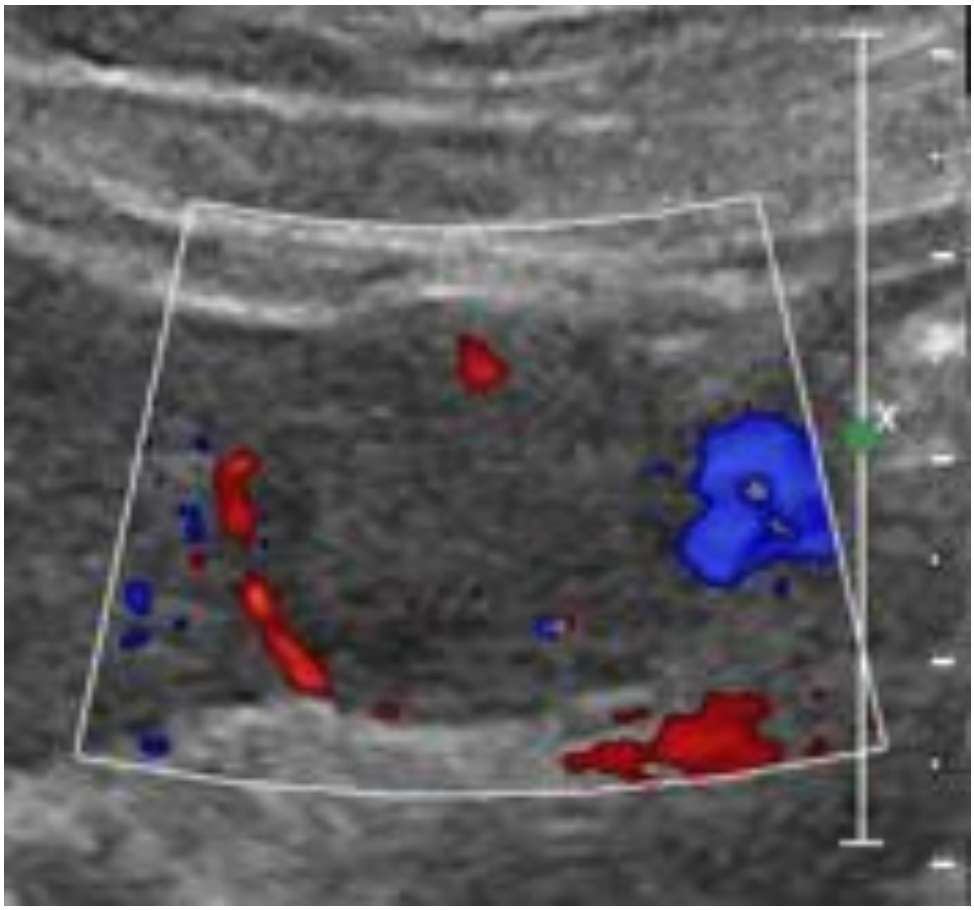


Fig 2: Left liver lobe showing a hypoechoic solid mass with increased vascularity

Image from https://pubs.rsna.org/author/Choi%2C+Jin-Young

1.3.2 ALPHA FETOPROTEIN

AFP is glycoprotein in blood that is used to detect preclinical HCC. High levels of AFP are normal in utero being secreted by yolk sac and fetal liver, which reduce to less than 10 ng/dl within 300 days of infancy. Subsequently high levels in serum suggest malignancy (30).

AFP can be used when imaging services are not available both as diagnostic tool and screening tool. HCC can produce significant levels of AFP more than 100000 ng/ml (26). In China, AFP levels of more than 400 ng/mL is used for diagnosis of HCC, although others disagree. It is limited since up to 40% of HCCs will have a normal level of AFP. AFP has a known variance between sensitivity and specificity (26). While specificity of AFP was almost 100% the sensitivity is as low as 45% (30). AFP is not accurate in detection of HCC. AFP has a low positive predictive value (PPV) ranging from 9% to 32% (30). The probability of picking HCC through AFP is low.

A prospective study done by Lai et al., (2017), where they followed up 26, 752 HBsAg carriers with AFP, only few AFP rise were seen among 61 men and 39 non-pregnant women. HCC diagnosis was made through ultrasound with 23 out of 32 patients having tumor size of less than 6cm.

The sensitivity of AFP as screening tool is low therefore not a good tool to use for HCC screening.

1.3.3 DESCARBOXY PROTHROMBIN

In 2017 Lai, Iesari, Battista, Sandri, & Lerut, (2017) did three selected studies, which showed the risk of HCC recurrence being 5 times. This means that DCP positive patients had 5 times risk of recurrence. DCP is not a useful screening tool but a diagnostic tool because elevation signifies vascular invasion meaning there is advanced stage HCC (9).

1.3.4 STUDY PREFFERED TOOLS

For this study we will use ultrasound as the screening tool which is non-ionizing radiation therefore safe to use. It's easily available and affordable. Those with liver lesions will be subjected to Tri phasic CT scan.

1.4 PROTOCOLS

According to Yilmaz, Yilmaz, Suer, Goral, & Cakir,(2018), most protocols for high risk patient to developing HCC were used across different countries.

North America use American Association for the Study of Liver Diseases (AASLD-2017). They do routine evaluation for high risk patients with cirrhosis, the first ultrasound done with or without tumor makers AFP every six months. This is according to the interval for screening being four to eight months and adjustments done in screening depending on the cause of liver diseases .Though 2011 guidelines recommended ultrasound scanning alone.

The Canadian Association for the Study of the Liver (CASL 2014): this report is from consensus conference updated of the existing consensus - CASL 2011. They are using AASLD 2011 guidelines- Ultra sound solely in every six months. The committee does not advise use of AFP either exclusively or incorporation with US due to low sensitivity of AFP at 67%. The cut off value for AFP being 200 ng/mL in liver cirrhosis. The best AFP sensitivity and specificity increased with optimal AFP serum levels of 20 ng/ml, Mehinovic et al., (2018) with AFP levels of 23.34 ng/ml had a high sensitivity of 84% and specificity of 82%.

Asia-The Asian Pacific Association for the Study of the Liver (APASL-2017): their recommendation is like AASLD utilizing both US and serum AFP measurement six monthly. The cut-off value of AFP being 200 ng/mL in case of liver cirrhosis.

For CHINESE-2017: updated from 2011. Their proposal for cirrhosis is like with APASL-2017 using both US and Serum AFP.

The Japan Society of Hepatology (JSH-2015): updated from 2013. They have a different guideline using ultrasound, AFP, a protein induced by lack of vitamin K or antagonist-II (PIVKA-II) and AFP-L3. It divides the group into 2 groups whereby they had a very high risk group and a high risk group. The first screening by Ultra Sound every 3-4 months along with three tumor markers (AFP, PIVKA-II and AFP-L3). The latter (patients with chronic hepatitis B, chronic hepatitis C, or non-viral cirrhosis) – Ultrasound screening done after six months

For the extremely high risk even with no evidence of tumor, there was addition of multi-detector computed tomography (MDCT) or MRI examinations in every 6-12 months.

The European Association for the Study of the Liver (EASL-2018): screening protocols recommended for Child-Pugh stage A and B patients, used Trans abdominal ultrasound every six months. Tumor makers AFP, AFP-L3 and DCP are not used due to less accuracy for early detection of HCC. Stage C cirrhosis not screened because of advanced disease except for transplant candidates

As seen above most of other guidelines recommended every six months follow up trans abdominal ultrasound to high risk patients with or without cirrhosis Though Spanish Society of Medical Oncology (SEOM)-2015, removed Child-Pugh C) patients from screening unless awaiting transplant.

There is a variety in protocol related screening preference from one region to another. The variance depends not only in the screening tool preferred but the type of risk to HCC presented as well as the severity of risk. For the purposes of this study we will use Ultrasound as a screening tool at time zero then recommend follow up every six months. The ultrasound will be

preferred because it has a high sensitivity, it's easily accessible, available and affordable compared to CT scan and MRI. Any lesions which will be detected by ultra sound will be subjected for further evaluation using Triphasic CT scan for confirmation.

1.4.1 TRI PHASIC CT SCAN

A 128 slice multi-detector CT scanner will be used with 120 Kv and a collimation of 1.5mm and a pitch of 1.88 will be used. It is confirmatory. Its limitations include; it uses ionising radiation, it's expensive compared to ultrasound, and someone can react to the contrast used.

The tri phasic CT scan will be pre contrast arterial phase and Porto venous phase;

1) Arterial phase HCC enhances vividly during late arterial phase around 35 seconds
2) Porto venous phase it washes out rapidly (hypo attenuating) 65 - 80 seconds

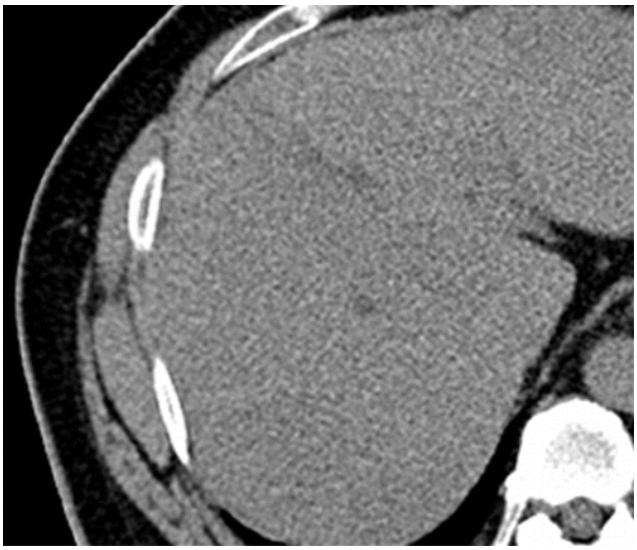


Figure 3(a): Images in a 51-year-old man with HCC and hepatitis B–related cirrhosis: multiphasic CT technique. There is no discernible lesion on pre contrast CT image.

Image from https://radiopaedia.org/users/jayanthmurthy?lang=us

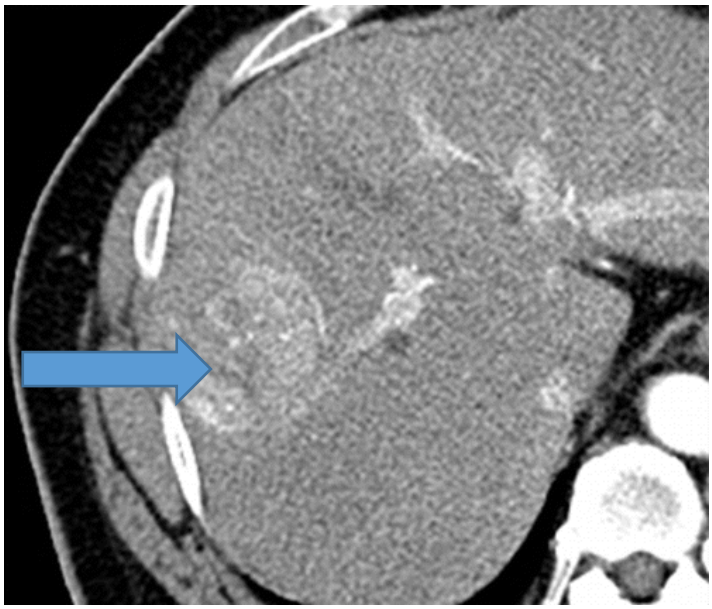


Figure 3(b) Late hepatic arterial phase image shows heterogeneously hyper enhancing mass with mosaic architecture in segment VIII.

Image from https://radiopaedia.org/users/jayanthmurthy?lang=us

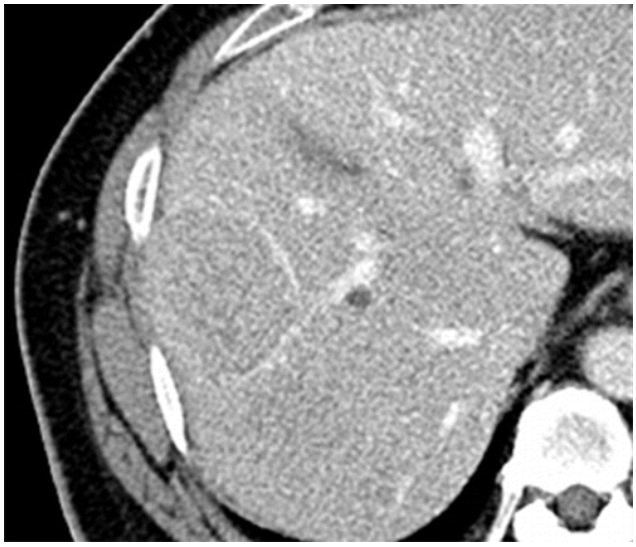


Figure 3(c) Relative to liver, mass de-enhances on portal venous

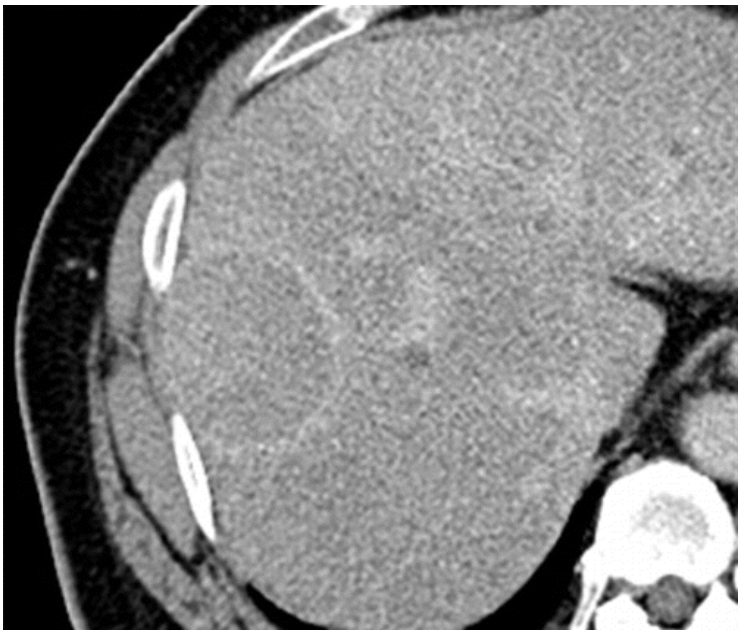


Figure 3**(d)** 3-minute delayed phase images to become iso attenuating with background parenchyma. Image from https://radiopaedia.org/users/jayanthmurthy?lang=us

1.5 PROBLEM STATEMENT

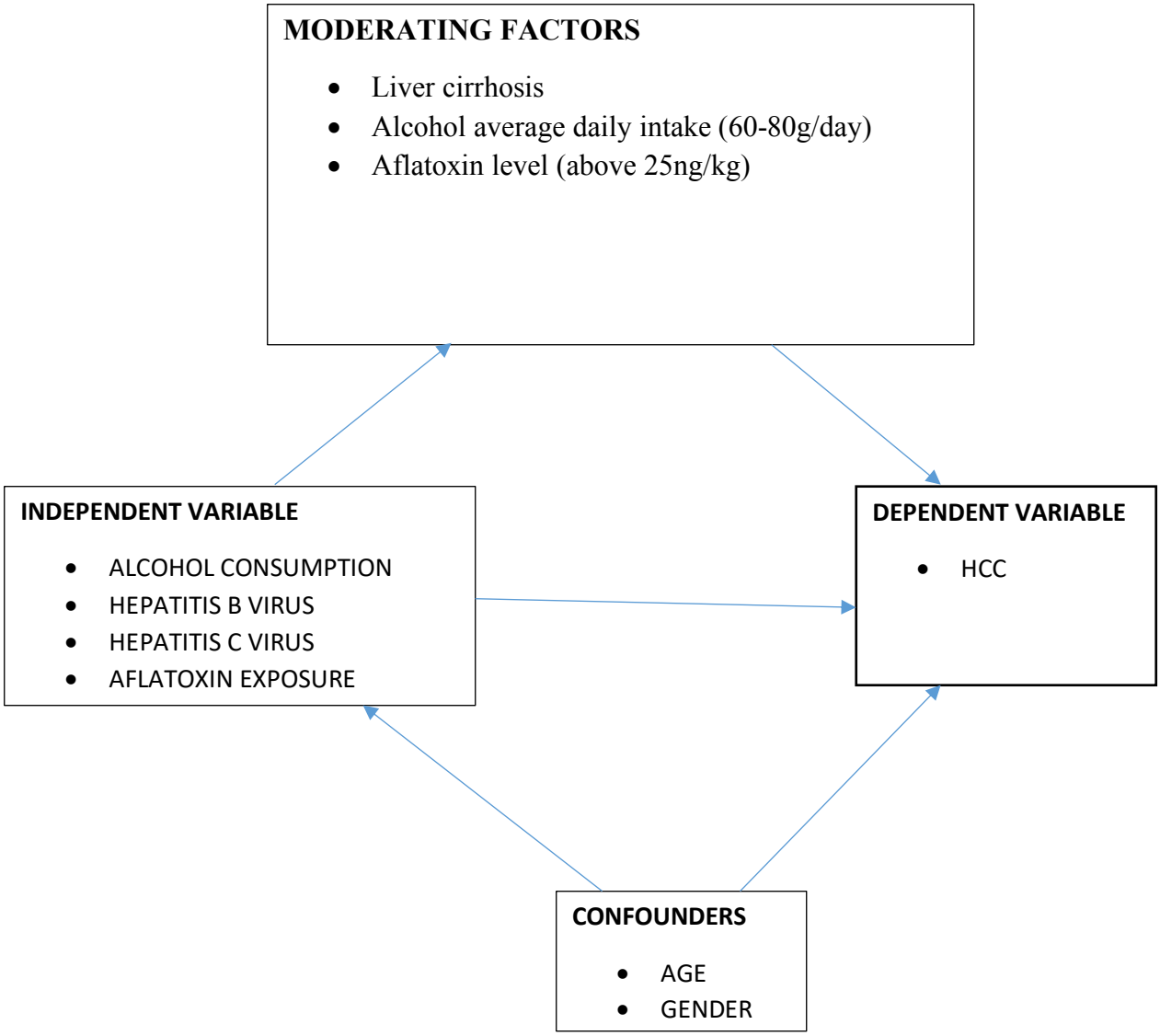
According to the regional cancer registry at KEMRI, about 80% of reported cases of cancer are diagnosed at advanced stages, HCC included. This is due to inadequate screening services, inadequate diagnostic facilities and poorly structured referral facilities among other reasons (49). Early and routine screening of HCC for high risk patients is important so as to decrease high cancer burden in Kenya.

However, with the regional diversity of risk factors and mixed findings on preferred screening tools, it is nearly impossible to arrive at a protocol that meets the need for early diagnosis and management. The aflatoxin in foods risk factor is prevalent in Eastern Kenya Makueni and Machakos (39). On the other hand HBV is prevalent in western region followed by

Mombasa then Nairobi. Ultrasound and Tumor makers α-fetoprotein (AFP) have shown good results in screening though AFP seems to have low sensitivity and is susceptible to other conditions. However, some protocols seem to prefer usage of the two for different reasons.

There is need of doing screening to all high risk patients and to come up with a screening protocol that meets the needs of the Kenyan population. This study seeks to investigate the prevalence of suspicious liver lesion among high risk populations and accuracy of ultrasound as a tool in screening of HCC.

1.6 CONCEPTUAL FRAME WORK



KEY

Independent: This is the risk factors or the "cause" of HCC

Dependent variable: This is the disease or health condition in this case number of HCC suspicious lesions in ultrasound vs Tri-phasic CT scan

Confounders: Affect the relationship between the independent and dependent variable directly, such that, their presence may either prevent or cause the outcome

Moderators: Are conditions under which the dependent variable is likely to generate the independent variable

2.0 CHAPTER TWO

2.1 JUSTIFICATION

There is increase in HCC prevalence yearly which increases disease burden and increase in mortality rate because of the diagnosis being made late in advanced stage. Kenya as a country doesn't have a screening protocol for the same hence there is need to develop and explore protocols for screening high risk populations at risk of developing HCC.

2.2 RESEARCH QUESTION

What is the prevalence of hepatocellular suspicious lesions and accuracy of ultrasonic screening in high risk patients attending liver clinic at KNH, in comparison to tri phasic CT scan?

2.3 BROAD OBJECTIVE

Determining the prevalence of hepatocellular suspicious lesions on ultrasonic screening in high-risk patients attending liver clinic at KNH and assign the positive of ultrasound findings a LI-RADS category on multiphasic CT examination.

2.3.1 SPECIFIC OBJECTIVES

1. To determine the prevalence of suspicious lesion on ultrasound in high risk populations in KNH
2. To assign the positive of ultrasound findings a LI-RADS category on multiphasic CT examination.
3. To determine the distribution of clinical risk factors among adults with suspicious HCC lesion

2.3.2 NULL HYPOTHESIS

The prevalence of hepatocellular suspicious lesions and diagnostic accuracy of ultrasound in screening for HCC in high risk patients is very low.

CHAPTER THREE

METHODOLOGY

3.1 Study design

The study was a cross sectional study which was carried out at the KNH liver clinic.

3.2 Study Area Description

The study was conducted in the liver clinic and at the radiology department of KNH.

3.3 Study population

The study included adults (above 18 years) who were at high risk of developing HCC. Those with Hepatitis B virus and Hepatitis C virus, history of chronic alcohol intake and aflatoxin exposure. Those patients referred from other hospitals.

3.4.0 Inclusion criteria

1. Any Adult (18 years and above) who came with a referral note from other hospital or from within KNH and not screened before.
2. Those referred to liver clinic because of high risk factors with the following laboratory results; HBsAg, HCsAg, Serum AFP and Serum DCP.
3. Those at risk of developing HCC with no known hepatic lesion at point of screening
4. Those with Child Pugh classification irrespective of the score.
5. Those who consented to take part in the study

3.4.1 Exclusion criteria

1. Those referred with known liver lesions like hemangioma, metastatic disease
2. Those who attended liver clinic but didn't have the HCC risk factors.

3. Those who refused to consent to take part in the study
4. Those who did not have CT scan done for any reason either cost or deranged Renal Function Test

3.5.0 Sample size determination

Sample size was calculated using Fisher's formula;

$$n = \frac{Z^2 x\ P(1-P)}{d^2}$$

Where,

n = Desired sample size

Z = value from standard normal distribution corresponding to desired confidence level (Z=1.96 for 95% CI)

P = expected true proportion (estimated at 19.7%, A retrospective study done at Moi Teaching and Referral Hospital in January 2010 to December 2012 showed a 19.7% prevalence of aflatoxin induced HCC.)

d = desired precision (0.05)

$$n_0 = \frac{1.96^2 x\ 0.197(1-0.197)}{0.05^2} = 243$$

A Sample size of 243 patients was required for the study.

The sample size was adjusted for finite populations less than 10,000

$$nf = \frac{n_0}{1 + \frac{n_0 - 1}{N}} = \frac{243}{1 + \frac{243 - 1}{168}} = 102$$

A Sample size of 102 patients was required for the study.

3.5.1 Sampling method

Convenience sampling methods was used where all patients who were found to have either of the risk conditions were sampled.

3.6 Study Procedure

The patients who presented the referral note or interdepartmental consultation note were booked for a liver clinic day.

The researcher went through all the referrals/ consultations notes in each file so as to identify the HCC high risk patients.

Those who met the inclusion criteria were approached by the researcher individually and explained for comprehensively why the research was being conducted and how they will benefit from it.

Those patients who accepted to take part in the research, were given a sociodemographic questionnaire to fill. They were given a radiological ultrasound request form which was ultrasound screening was done at day 0. The screening was done by the researcher and the sonographers at KNH room 33 who are well trained and experienced using a curvilinear probe 3.5-5MHZ using GE logic P6 ultrasound machine.

With the patient is supine position, the scan was done from the right side of the patient. Sagittal images were taken with the indicator of the probe directed towards the patients head at the midline so as to get the left lobe of the liver.

To evaluate the right lobe of the liver the probe was placed along mid clavicular and the indicator directed towards the patient's right. The following was looked at since HCC has a variety of appearances on ultrasound;

1) Massive (focal) large mass which will be heterogeneous
2) Nodular (multifocal) multiple masses -hypoechoic
3) Infiltrative (diffuse)- difficulty to identify or distinguish in the background of cirrhosis

Those participants who were ultrasound negative i.e. free of liver lesions; were followed up after six months through Liver clinic.

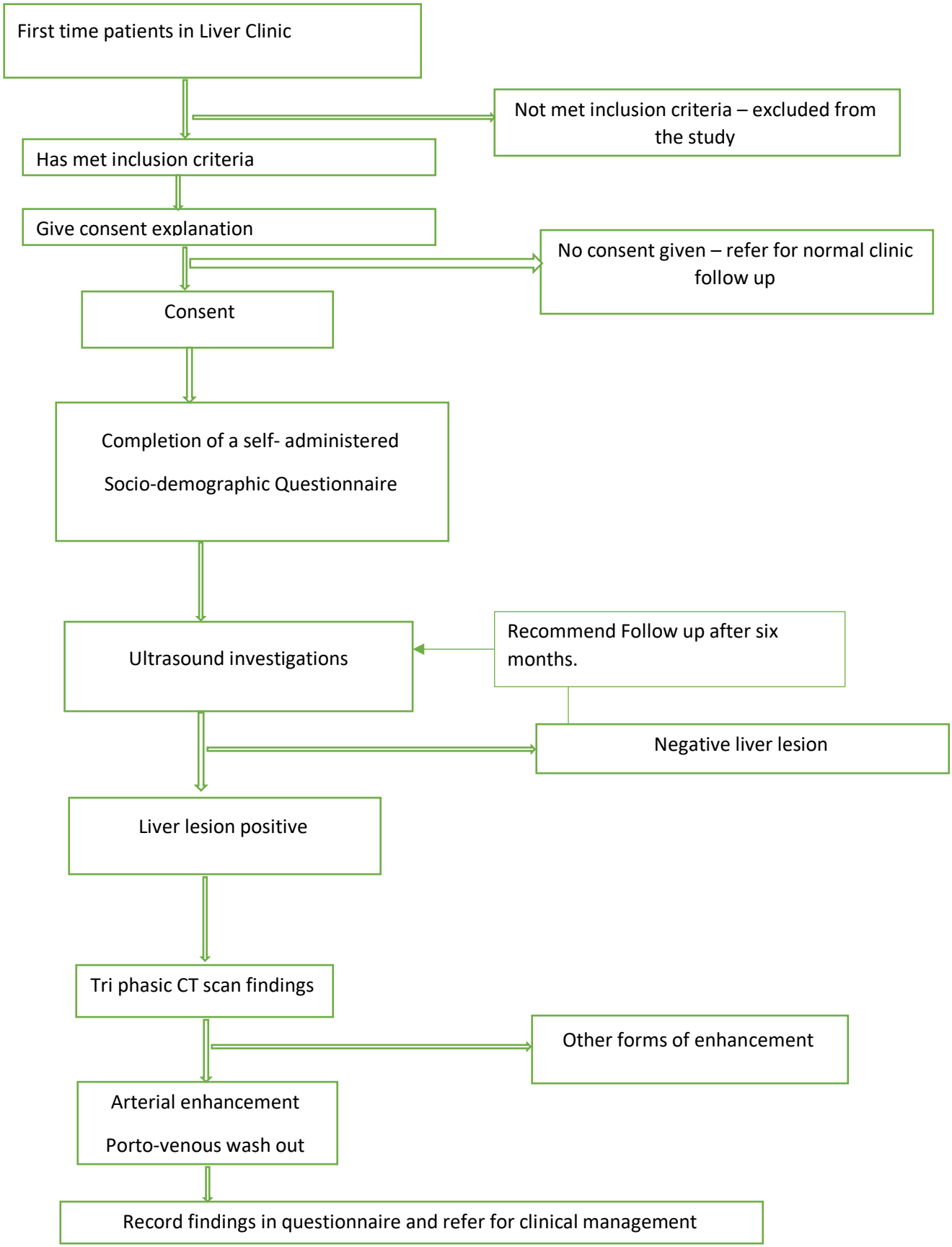
Those who had some liver lesion picked, measuring more than 10mm in the background of cirrhosis, were subjected for further imaging evaluation with Tri phasic CT scan. A 128 slice multi-detector CT scanner was used with 120 Kv and a collimation of 1.5mm and a pitch of 1.88. The tri phasic CT scan was pre contrast arterial phase and Porto venous phase; on late arterial phase HCC enhanced vividly around 35 seconds and washed out on porto-venous phase (hypo attenuating) 65 - 80 seconds

Correlation between the ultrasound picked liver lesions with the Tri-phasic CT scan, was made.

Those patients who were found with liver lesions were referred for routine Interventional Radiology clinic follow up.

Those diagnosed with HCC were managed according to the guidelines described under the introduction and literature section.

3.7.0 Consenting and Data Collection Flow Chart



3.7.1 Study Materials

A questionnaire which captured age, sex, chief complaint, onset of illness, clinical symptoms like jaundice (yellow eyes), laboratory findings (HBsAg) family history of liver disease, alcohol history, and blood transfusion history among other sociodemographic information.

The researcher used General electric ultrasound using GE logic P6 pro, curvilinear probe with low frequency 3.5-5-MHz,

Figure 4; GE logic P6 pro.

Source; KNH, ultrasound room 33

Positive results were determined from the ultrasound findings in the form of the hypoechoic multifocal lesions or the heterogeneous focal lesion measuring more than 1cm.

A 64 slice multi-detector CT scanner was used with 120 Kv and a collimation of 1.5mm and a pitch of 1.88 was used. In the tri phasic CT scan, researcher was looking out for the enhancement pattern showing vividly enhancement (hyper attenuating) in late arterial 35seconds and early wash out (hypo attenuating) in Porto venous 65 to 80 seconds.

Figure 5: CT scan machine

3.7.2 Study personnel

The researcher was a student pursuing a Masters of Medicine in Diagnostic Imaging and Radiation Medicine.

The main role of the investigator was to identify the high-risk patient from the liver clinic and do the ultrasound scanning to the patients.

3.8 DATA MANAGEMENT AND ANAYLYSIS

3.8.1 Data Collection Tool

Patient history, ultrasonic suspicious lesion and tri-phasic CT scan findings was documented on a data collection sheet and subsequently the information was fed into a computerized data base.

3.8.2 Data Management Plan and Analysis

Data was entered and analyzed using Statistical Package for Social Sciences (SPSS) version 23. Demographic characteristics were analyzed and presented as frequencies and proportions for categorical data, while continuous data was presented as mean and standard deviation. The prevalence of suspicious lesion was reported as a proportion of the total of the sample patients in the study with suspicious lesions on ultrasound examination. The distribution of the clinical risk factors among adults with suspicious HCC lesion was reported as frequencies and proportions. Where applicable, p values of <0.05 was considered significant for all tests at a confidence interval of 95 percent.

3.9 Quality assurance protocol

Quality assurance was an integral part of clinical care and especially in sonography which was a high operator and technique dependence. The scans were done by the principal investigator by ensuring that the ultrasound findings are reproducible.

Three measurements of any liver lesion picked were done and a mean value calculated. All the liver lesions picked on ultrasound were further examined using Tri phasic CT scan and the images were read by the principle investigator and the supervisors.

Both images from ultrasound and CT scan, were stored in soft copy and reviewed on a weekly basis by a consultant radiologist.

3.10 Ethical considerations

Written informed consent was sought from the participants after comprehensive explanation was done.

Ethical clearance was obtained to conduct this study from KNH/UON Ethics and scientific Review committee.

Institutional permission was sought from both KNH research department and UON department of diagnostic imaging

Departmental permission was sought from the Liver clinic and radiology department.

No examination was carried out on the patients other than the one requested from the clinic

There were no risk factors associated with ultrasound as a screening tool, since ultra sound does not use radiation. Therefore safe to be used as a screening tool.

Tri phasic CT scan was only done for those patients who needed further evaluation of the lesion picked by ultrasound.

Any diagnostic information which was found to be beneficial to the patient was shared with the managing team to aid with the management of the patient appropriately.

3.10.0 Confidentiality of the participants

The principal investigator ensured that there were no identifiers that could link the research data to the study participants. Each study participant was allocated a unique numeric identifier that was used in data abstraction and data base. However, a link log was used to ensure follow up of patients who needed to be followed up for further clinical management.

3.10.1 Privacy of data obtained

The results were submitted to the university radiology department where no unauthorized persons would have access to the data. The questionnaire the researcher used a unique identifier like codes. The data was analyzed using the codes too.

3.10.2 Data Dissemination

The findings of the study were given to Kenyatta National Hospital and University of Nairobi for future reference and patients care. The findings was also going to be published in peer review journals, technical briefs and presentation in Kenyan and international forums.

CHAPTER 4

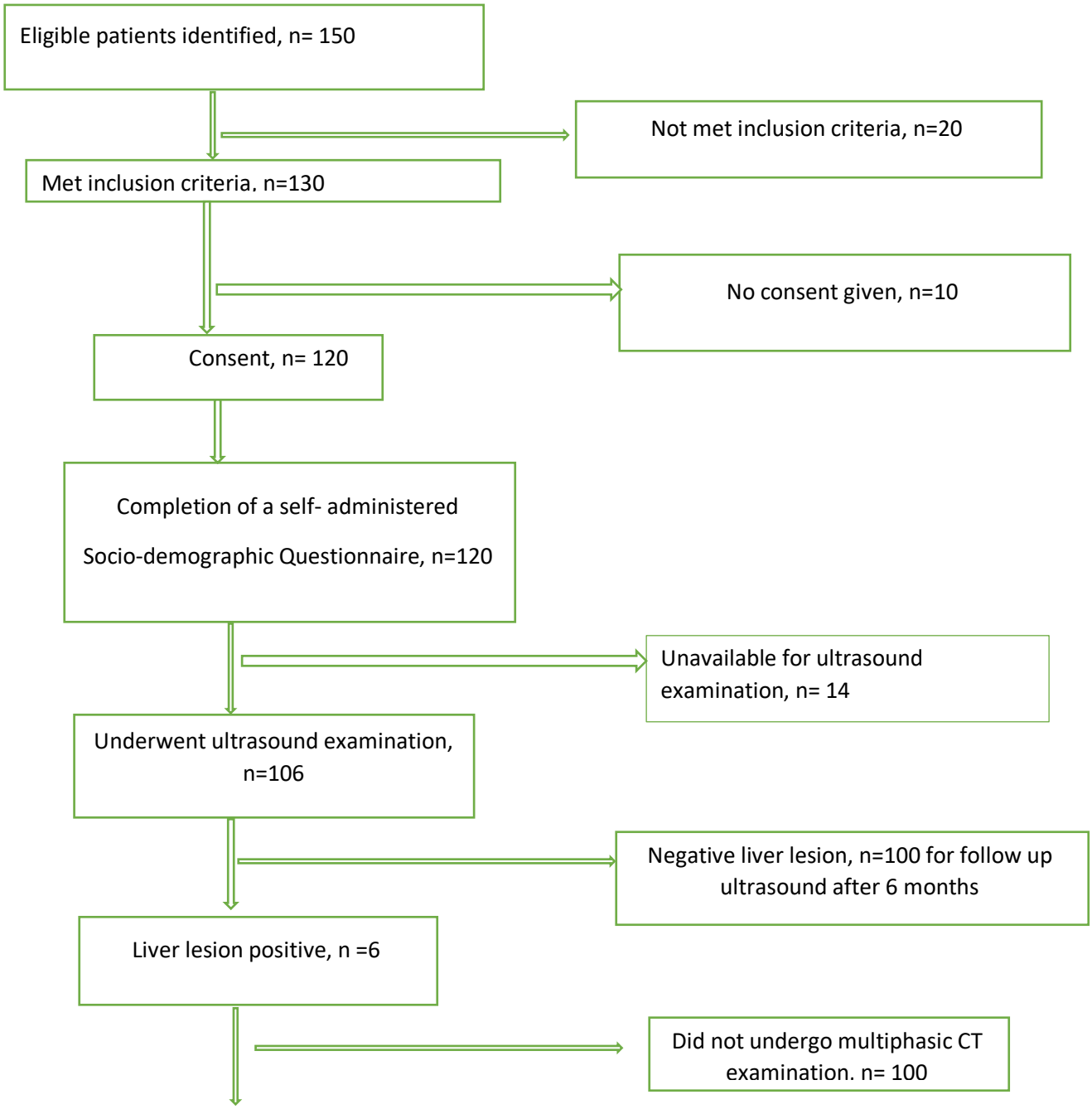
RESULTS

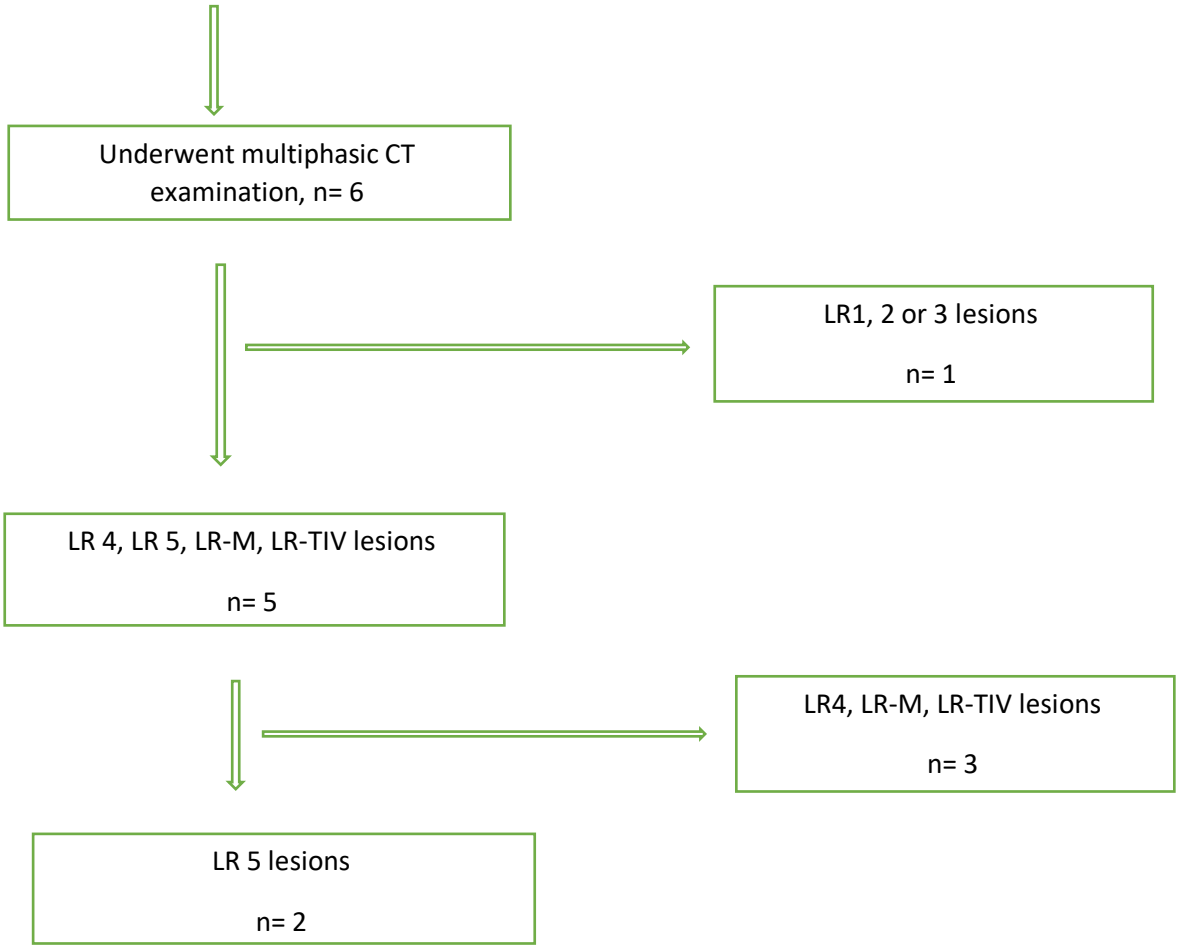
4.1 Introduction

The results of the study are presented in this chapter.

SUMMARY OF RESULTS

The summary of results are presented in a flow chart below.




Underwent multiphasic CT examination, n= 6
LR1, 2 or 3 lesions
n= 1
LR 4, LR 5, LR-M, LR-TIV lesions
n= 5
LR4, LR-M, LR-TIV lesions
n= 3
LR 5 lesions
n= 2

4.2 Socio Demographic Characteristics of the Patients

The mean age of the patients was 39.4 (SD 12.8) years, while the median age was 37.5 (IQR 29.0 – 46.0) years. The minimum age was 14 years while the maximum age was 82 years. There were 65 (61.3%) male patients, while 41 (38.7%) who were female. Majority of the patients were from Nairobi (80, 75.5%).

Table 1.0: Socio Demographic Characteristics of the Patients

Age (Years)	**Frequency (N=106)**	**Percentage (%)**
≤20	2	1.9
21-30	25	23.6
31-40	35	33.0
41-50	24	22.6
51-60	15	14.2
>60	5	4.7
Gender		
Male	65	61.3
Female	41	38.7
County		
Nandi	3	2.8
Makueni	2	1.9
Nairobi	80	75.5
Muranga	3	2.8
Kitui	3	2.8
Machakos	2	1.9
Kiambu	6	5.6
Nyandarua	1	0.9
Nyeri	1	0.9
Mombasa	1	0.9
Tharaka Nithi	1	0.9
Busia	1	0.9
Meru	1	0.9

Lamu	1	0.9

4.3 Presenting complaint and Laboratory Results

The past medical history of the patients indicated that out of the 106 patients, 29 (27.4%) had a complaint of yellow eyes and abdominal distention, 23 (21.7%) had abdominal distention only, while 15 (14.2%) had yellow eyes only. This is as shown on Table 2.

Table 2.0: Chief Complaint

	Frequency (N=106)	Percentage (%)
Yellow eyes	15	14.2
Abdominal distention	23	21.7
Both	29	27.4
None	39	36.8

The laboratory results indicate that 75 (70.8%) of the patients had positive HbsAg results. On the HCsAg test, 4 (3.8%) of them had positive results. This is as shown on Figure 1.0

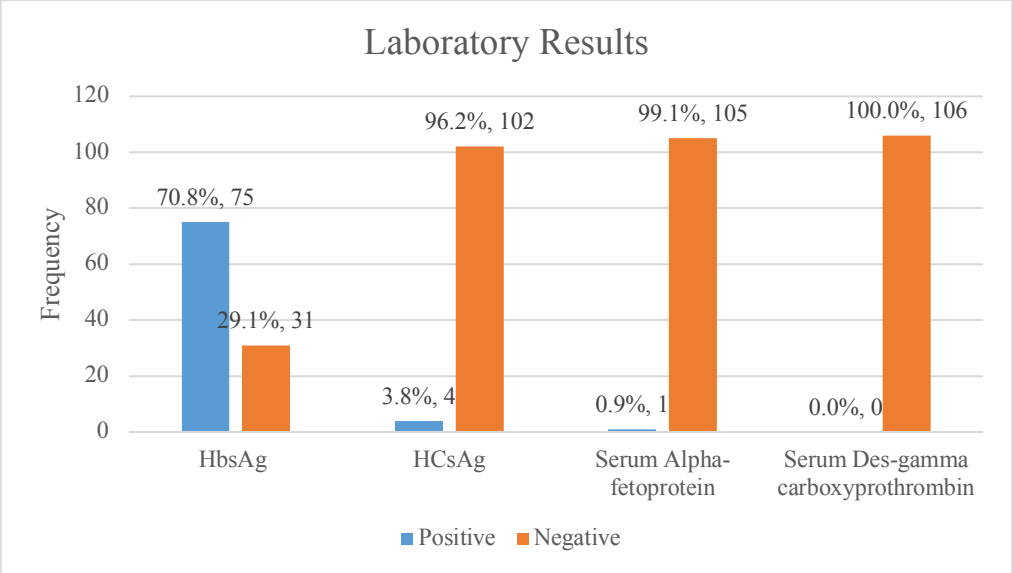


Figure 1.0: Laboratory Results

There was only 1 (0.9%) patient who had a family history of liver disease. On the history of alcohol intake, 43 (40.6%) of them had a history of alcohol intake. None of the patients had contact with someone with Hepatitis. Eighteen (17.0%) of them had a prior blood transfusion. This is as shown on Table 3.

Table 3.0: Family Social History

	Yes, n (%)	**No, n (%)**
Family history of liver disease	1 (0.9)	105 (99.1)
History of alcohol intake	43 (40.6)	63 (59.4)
Contact with someone with Hepatitis	0 (0.0)	106 (100.0)
Had a blood transfusion	18 (17.0)	88 (83.0)

The results on Table 4 show the sources of the food the patients had access.

Table 4.0: Sources of Food

	Yes, n (%)	**No, n (%)**
Processed	106 (100.0)	
Maize	106 (100.0)	
Rice	106 (100.0)	
Groundnuts	104 (98.1)	2 (1.9)
Milk and milk products	106 (100.0)	

4.4 Clinical Diagnosis

On the Hepatitis diagnosis, Figure 2.0 shows that 77 (73.0%) of the patients had Chronic Hepatitis, and of these patients, 73 (94.8%) it was secondary to Hepatitis B virus, while for only 4 (5.2%) it was secondary to Hepatitis C virus as shown on Table 5.0.

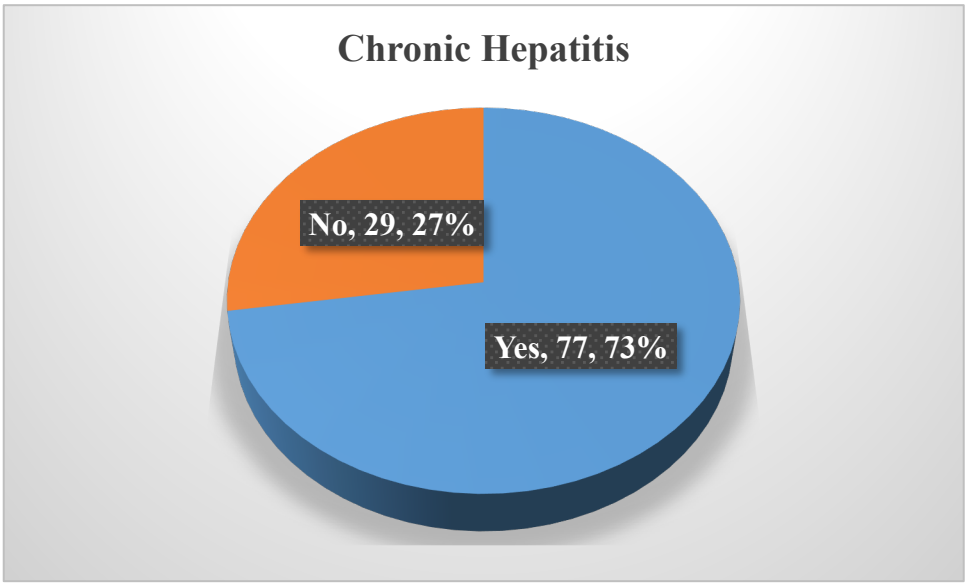


Figure 2.0: Diagnosis of Hepatitis

Table 5.0: Type of Hepatitis Diagnosis

	Frequency (n=77)	Percent
Hepatitis B virus	73	94.8
Hepatitis C virus	4	5.2

There were 29 (27.0%) patients who had a clinical diagnosis of Liver Cirrhosis of all the patients, and this is as shown on Figure 3.0.

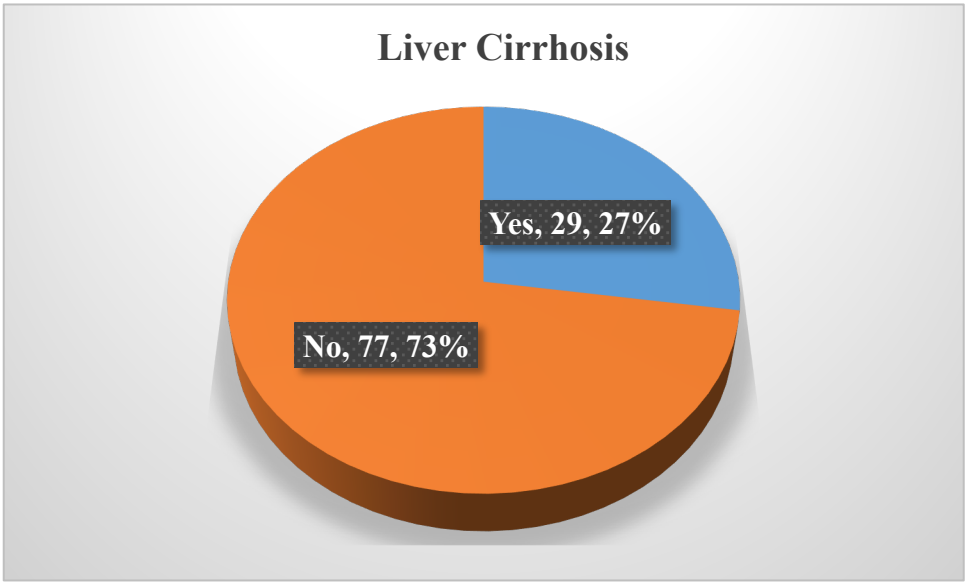


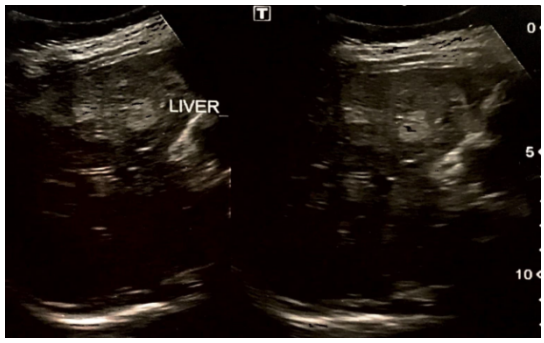
Figure 3.0: Diagnosis of Liver Cirrhosis

4.5 Ultrasound Findings

The ultrasound findings from the 106 patients reveals that 29 (27.4%) of the patients had a diagnosis of liver cirrhosis, of which only six of them had liver lesions where 4 had solitary, multiple and diffuse lesions were seen in one patient each. On the echo pattern, all the 6 were homogenous, of which three were hypoechoic and three were hyperechoic. The size for all the 6 were above 10mm.

Table 6.0: Ultrasound Findings

Liver cirrhosis	**Frequency (n=106)**	**Percent (%)**
Yes	29	27.4
No	77	72.6
Liver lesions		
Multiple	1	0.9
Solitary	4	3.8
Diffuse	1	0.9
None	100	94.4
Echo pattern		
Homogenous	6	5.6
None	100	94.4
If yes (Homogenous)		
Hypoechoic	3	2.8
Hyperechoic	3	2.8
None	100	94.3
Size		
>10mm	6	5.6
None	100	94.4

a 

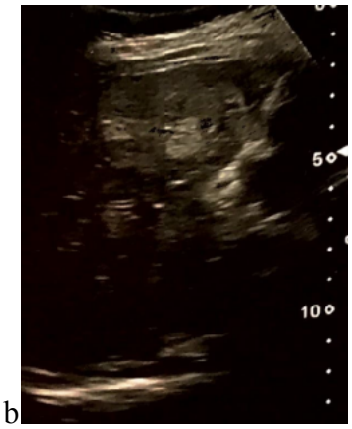
b 

Figure 4.0 a and b

Gray scale image of the liver demonstrating nodular surface with multiple well defined hyper echoic lesions.

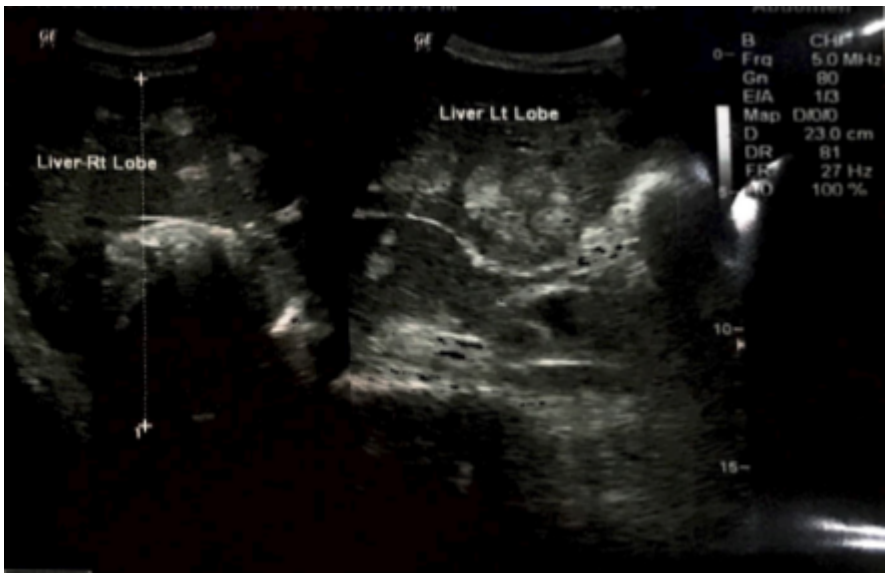
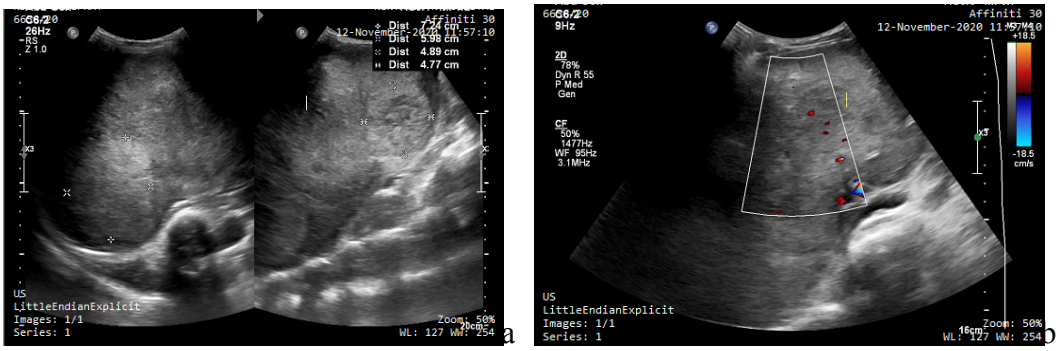


Figure 5.0

Gray scale image of the liver demonstrating multiple lobulated hyper echoic lesion, with ascites.

The distribution of the ultrasound diagnosis of the patients revealed that of the 106 patients, 25 (23.6%) had liver cirrhosis, 10 (9.4%) had hepatitis, 6 (5.6%) had liver lesions, and the rest of the patients (61, 57.5%) had normal findings.



a b

Figure 6.0 a and b

Gray scale image of the liver demonstrating multiple lobulated hyper echoic lesion, with internal vascularity on colour Doppler.

Table 7.0: Ultrasound Diagnosis

	Frequency (n=106)	Percent (%)
Normal	61	57.5
Liver cirrhosis without lesions	25	23.6
Fatty liver	4	3.8
Hepatitis	10	9.4
Liver lesions	6	5.6

The distribution of the CT scan findings of the patients revealed that only six of the106 patients had undergone a CT scan, of which five of them had multiple liver lesions while one patient had infiltrative diffuse liver lesion. The results of the findings are as shown on Table 8.

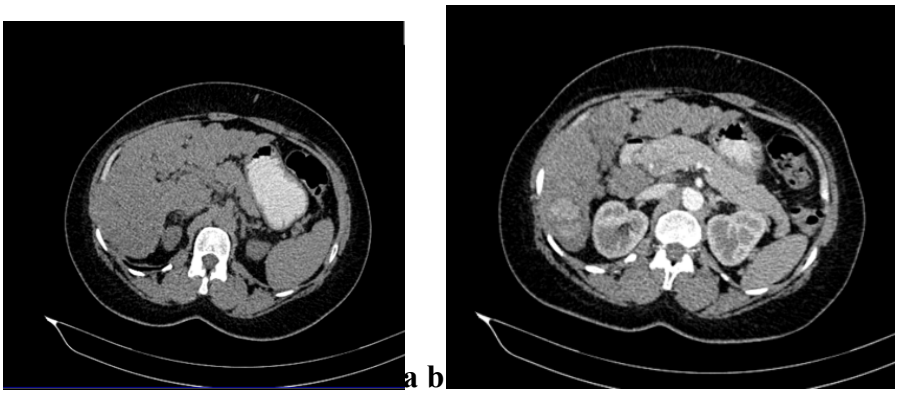
Table 8.0: CT scan findings

	Frequency (n=106)	Percent
Liver lesions	6	5.6
Not done	100	94.4

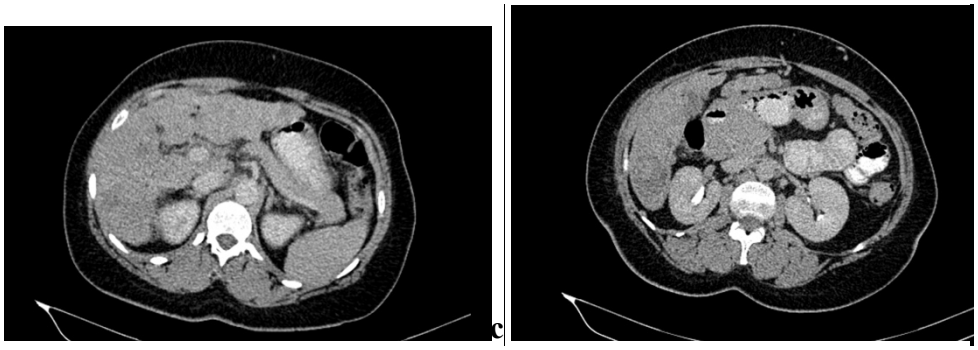
The results of the triple phase findings and for the patients with the liver lesions found on ultrasound is as shown on Table 9. The table lists each of the 6 patients and the enhancement pattern findings and LI-RADS (LR) classification. Two patient LR 5 (definite HCC), one patients LR 4 (probably HCC), two with LR-M, and one patient LR 3 (intermediate).

Table 9.0: Triple Phase CT Findings

Patient	No of lesions	Size of lesion(s)	Enhancement pattern				Vascular involvement	LR Category
			Precontrast	Arterial	Portal venous	Delayed		
1	5	1-2cm	hypodense	Hypo attenuating	Hypo attenuating	-	None	LR-M
2	1 lobulated	> 6cm	isodense	heterogenous	Patchy washout	-	Right hepatic artery	LR-4
3	1 infiltrative	>6cm	Isodense	Patchy	washout	-	Portal vein	LR-5
4	1	5cm	hypodense	Peripheral	none	Hyper attenuating	none	LR-3
5	1	4cm	Isodense	avid	washout	Hypo attenuating	none	LR-5
6	1	2cm	hypodense	none	No enhancement	Some enhancement	none	LR-M

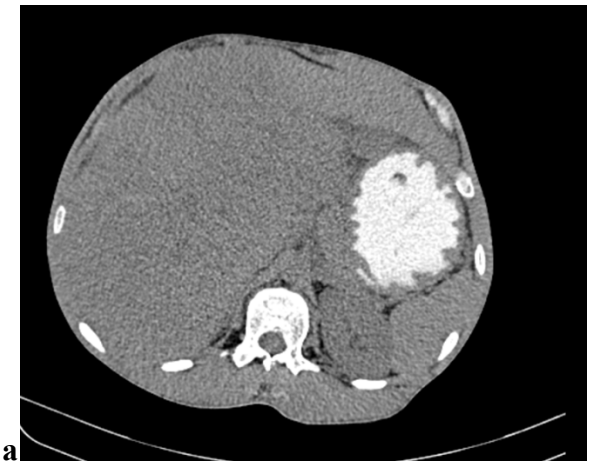


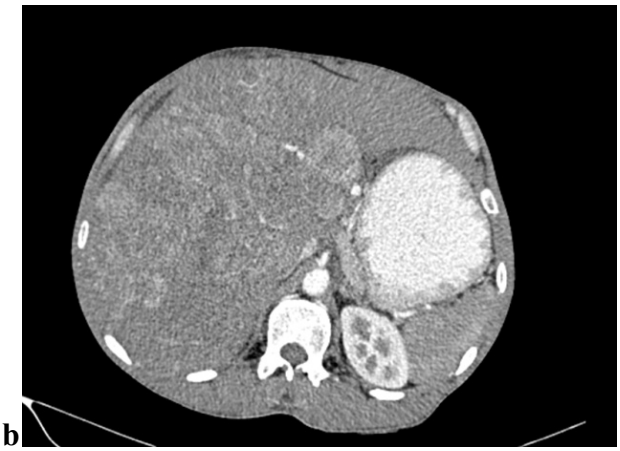
a b



c d

Figure 7; LIRADS 5 Axial CT scan images a-pre-contrast, b-d post contrast; b-arterial phase, c-Porto-venous phase, d-delayed phase. The images demonstrates a nodular surface contour, with a lesion in segment vi which is isodense to the liver in (a), avid contrast enhancement in (b), washout in (c), hypo attenuating (d).

a 

b 

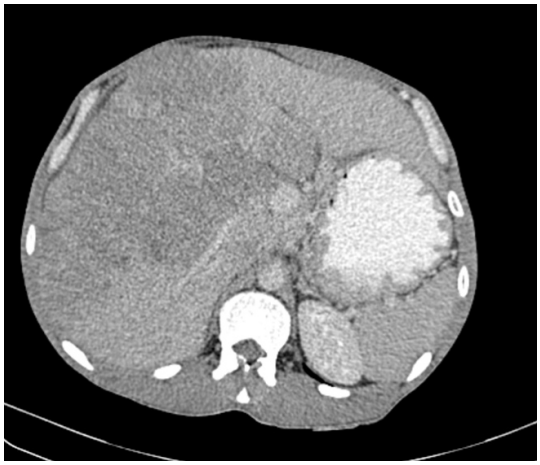
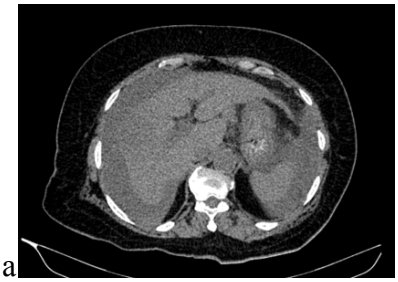
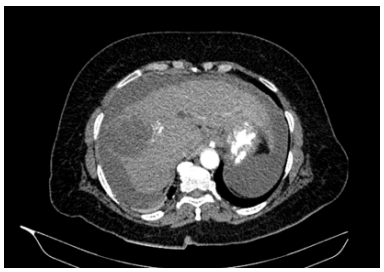
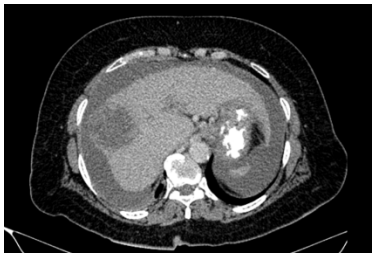
c 

Figure 8; LR-5 Axial CT scan images a-pre-contrast, b-arterial phase, c-Porto-venous phase.

The images demonstrate multifocal lesion, it is iso-dense (a), heterogeneous patchy contrast enhancement (b), wash out (c), and there is involvement of hepatic artery.

a  b  c 

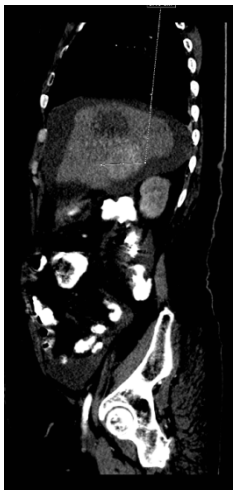
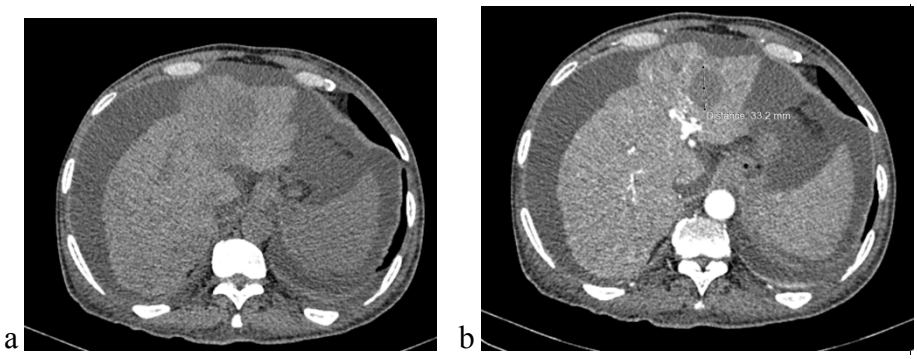
d 

Figure 9; LIRADS 3 Axial CT scan images a-pre-contrast, b-arterial phase, c-Sagittal reformatted delayed.

The images demonstrate features of cirrhosis with ascites. There is sub-capsular lesion in the segment viii, it is hypodense (a), peripheral contrast enhancement (b), and progressive peripheral enhancement with central non-enhancement (c).



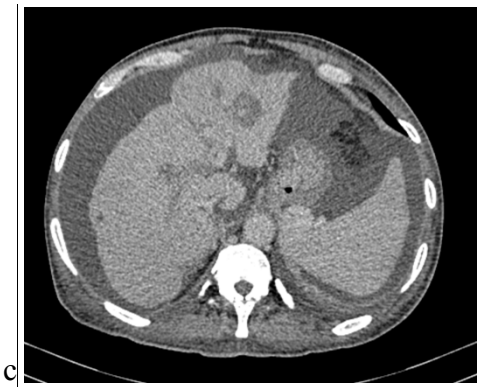
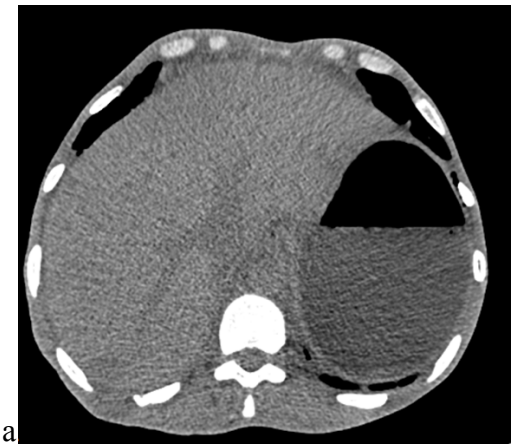
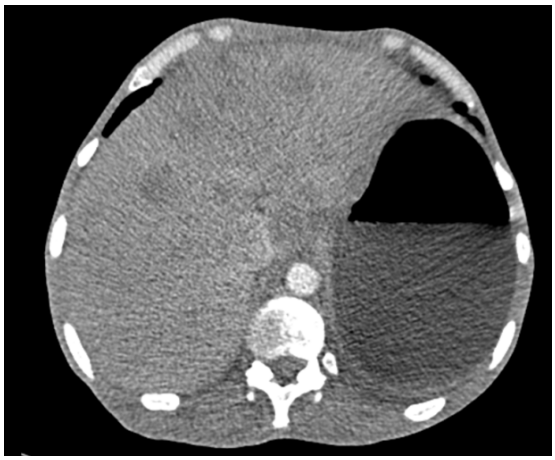


Figure 10; LR-M Axial CT scan images

A-pre-contrast, b-arterial phase, c-delayed. The images demonstrate features of cirrhosis-nodular contour and shrunken with ascites.

There is a well-defined round lesion which is hypodense (a), no contrast enhancement (b), enhancement of central nodule (c)

a  b 

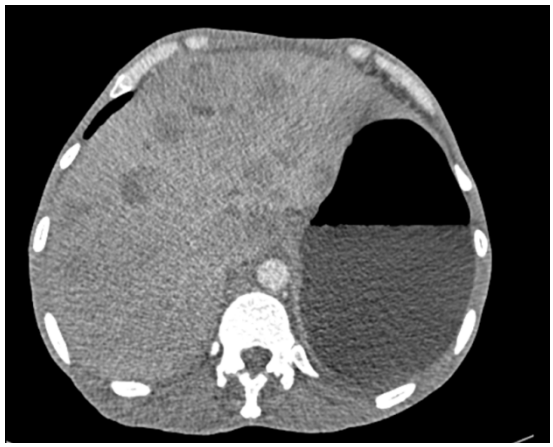
c 

Figure 11; LR-M Axial CT scan images a-pre-contrast, b-arterial phase, c-Porto-venous phase. There are multiple hypo attenuating hepatic lesions.

Table 10.0: CT Scan finding with liver lesions

	Diffuse liver lesions	Nodular liver lesions
Hepatitis B	0	4
Hepatitis C	0	0
Other (Alcohol intake)	1	1
Total	1	5

Table 11.0: Liver lesions against viral hepatitis

The results on Table 11 indicate that four of the six patients' cause of liver lesions had Hepatitis B infection, while the other two were non-viral hepatitis related. There was no statistical significance p-0.998.

	Lesions on ultrasound	No lesions on ultrasound	p-value
Viral hepatitis	4	71	0.998
Non-viral liver disease	2	29	

Table 12.0: Liver lesions against cirrhotic liver

The results on Table 12 revealed that four of the six lesions occurred in a cirrhotic liver, while the rest 2 was in non-cirrhotic liver. From the 2 tables 11 and 12 the four patients had both viral hepatitis and liver cirrhosis. Twenty five patient despite having liver cirrhosis had not developed liver lesions. Most of the lesion detected had cirrhosis but there was no statistical significance ($p = 0.332$).

	Lesions on ultrasound	No lesions on ultrasound	p-value
Cirrhotic patients	4	25	0.332
Non-cirrhotic patients	2	75	

Table 13.0: Correlation of risk factors and lesions

Two of the six patients who had a history of alcohol intake were found to have lesions on ultrasound, whereas one of the six had a family history of liver disease, four had viral hepatitis, and one had a past blood transfusion (p-0.997, p-0.998 and p-0.999) respectively. This is as shown on Table 13.

	Lesions on ultrasound (n=6)	No lesions on ultrasound (n=100)	p-value
Family history of liver disease	1	0	0.057
History of alcohol intake	2	41	0.997
Viral hepatitis	4	71	0.998
Had a blood transfusion	1	17	0.999

Table 14.0 Correlation of alcohol risk factor and LIRADS

Two of the six patients who had a history of alcohol intake were found to have lesions on ultrasound, given the LIRADS classification one had LIRAD 1(benign lesion) and one had LIRAD IV (probably HCC), p -0.996 was statistically insignificant.

	LI-RADS I, II	LI-RADS III	LI-RADS IV and V	p-value
Family history of liver disease	0	0	0	-
History of alcohol intake	1	0	1	0.996
Contact with someone with Hepatitis	0	0	0	-
Had a blood transfusion	0	0	0	-

Table 15.0: Comparison of characteristics of lesion with LIRADS classification.

The study revealed that participants who were diagnosed with liver cirrhosis developed lesions which had a higher LIRAD classification, the higher the class the more likely the lesion was HCC, p-0.067.

The non-cirrhotic had intermediate findings LIRADS CLASS III

	LI-RADS I, II	LI-RADS III	LI-RADS IV and V	p-value
Cirrhotic patients	0	0	3	0.067
Non-cirrhotic patients	0	1	0	

Chapter 5

DISCUSSION

The study demonstrated that ultrasound could detect liver lesions amongst high risk patient for HCC. The lesions were correlated with tri-phasic CT scan and three of the lesion were highly suspicious of HCC LIRADS 4 and 5.

The study found that the prevalence of suspicious lesion on ultrasound in high-risk populations in KNH was 5.6%. Of the lesions detected 3 (2.8%) were malignant suspicious of HCC, 2(1.9%) were definite HCC. On ultrasound they were heterogeneous and predominantly hyperechoic measuring more than 10mm. Teerapat et al 2016 in their study found a prevalence of 3.3 % in patients who had chronic Hepatitis B, which was demonstrated by the liver having increased echogenicity and heterogeneous echotexture and liver cirrhosis, this is almost comparable to this study finding (12).

Each lesion was given a LI-RADS category, one lesion had intermediate probability for HCC. In tri-phasic CT scan three lesions were hypodense and three were iso-dense to the liver parenchyma in pre-contrast images. For the LR 4 and 5 lesions, two demonstrated avid contrast enhancement in arterial phase with washout in Porto-venous phase with the remaining one showing partial wash out. Saar et al 2008, demonstrated that typical HCC showed avid arterialization and contrast wash out in late Porto-venous contrast phase, which was the case for one lesion demonstrating features of definite HCC- LIRADS 5(27). Balogh et al showed the same thing avid enhancement in arterial phase and hypo-attenuating on portal phase (28). It was also noted that the three participant with LIRADS 4 and 5 had very high values of Hepatitis B viral load count which were 55,202 iu/ml, 817,359 copies/ml, and 53,493 iu/ml. Some patients

on follow up had Hepatitis B viral load as low as 61 iu/ml with normal trans-abdominal ultrasound findings.

Clinical risk factors among adults with suspicious HCC lesion infectious causes mainly was Hepatitis B virus followed by Hepatitis C virus with cirrhosis which was comparable with Teerapat study(12). The laboratory results indicate that 75 (70.8%) of the patients had HbsAg and 4 (3.8%) Hepatitis C core Ag positive results. On the non-infectious causes alcohol was leading. Out of the 75 participants on follow up for Hepatitis, 4 patients were found to have liver lesions on ultrasound. This is was contrary to a study done in United States by El-Serag et al 2014 which showed that the risk of developing HCC was higher with Hepatitis C at 50%-60% then followed by Hepatitis B at 10-15%. The findings were the same for non-infectious causes, alcoholic liver disease leading at 20%-25 %(29).

The ultrasound findings from the 106 patients reveal that 25 (23.6%) of the patients had a diagnosis of liver cirrhosis which is a risk factor of developing HCC.

There was a role of cirrhosis in developing HCC in both infectious and non-infectious causes. This was demonstrated in our study though with a lower percentage, as four (3.75%) of the six patients who had liver lesions had liver cirrhosis. A study done by Hassan et al, 2002 established that 60-80% of HCC had cirrhosis, 69% of the HCC patients had chronic hepatitis C virus and 5% chronic hepatitis B (30) while Maponga et al also established that 23% of the HCC patients had cirrhosis (31).

In this study the distribution of risk factor, there was predominance of male than female at 61.3% and 38.7% respectively. A study done by Hassan et al, 2002 had a sample size of 115 most of the

affected subject were male at 75.7% and female at 24.3 %(30). According to Raphael et al 2013, also demonstrated male were more affected at 84.2 %(32).

Some important limitations of this study was, being cross-sectional as a baseline survey, whereas a longitudinal study for a longer duration can provide information about the HCC incident rates. However, the strength of it is that we demonstrated that it is possible to practically run the entire radiological HCC screening process in our apparently low resource setting.

We did not correlate the LR 3, LR-4 and LR-M lesions with histology for complete diagnostic closure but we of course recommended the same. We also hope to capture the radiological diagnosis in a follow up study consisting of a larger sample of such lesions.

There was no correlation with AFP level as a screening tool with the ultrasound as it was not routinely used.

5.1 Conclusions

Our study demonstrated a prevalence of suspicious lesions of 5.66%. Multiphasic CT was capable to correctly characterize all of them with 1.9% showing features of definite HCC and 2.8% were malignant suspicious of HCC.

It also demonstrated that a well-organized radiological diagnostic pathway can be achieved in HCC screening even in a lower middle income country like Kenya.

5.2 Recommendations for Further Research

The study recommends that for the high risk patients a screening program should be established in Kenya.

To do a longitudinal study for a longer duration in order to have local statistics which can aid to validate LIRADS in our population.

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APPENDICES

APPENDIX 1: Data collection tool

ULTRASOUND IMAGING DETECTION OF HEPATOCELULAR SUSPICIOUS LESION AMONG HIGH RISK PATIENTS ATTENDING KENYATTA NATIONAL REFFERAL HOSPITAL

Principal investigator: Dr Malindi Ephranzia Chao

1. **<u>Socio-Demographic Questionnaire – Researcher administered</u>**

STUDY CODE: _____

SEX (tick where appropriate): Male ☐ **Female** ☐

AGE (in completed years): _____

Residence: Nandi ☐ Makueni ☐ Nairobi ☐ **Others:** _____

2. **Chief complaint:**

Past Medical History:

Yellow eyes **(tick where appropriate)** YES ☐ NO ☐

Abdominal distension **(tick where appropriate)** YES ☐ NO ☐

3. **Laboratory results:**

HBsAg normal **(tick where appropriate)** YES ☐ NO ☐

If abnormal state the values

HCsAg normal **(tick where appropriate)** YES ☐ NO ☐

If abnormal state the values

Serum Alpha-fetoprotein (AFP) Normal YES ☐ NO ☐

If abnormal state the values

Serum Des-gamma carboxyprothrombin (DCP) Normal ☐ YES ☐ NO

If abnormal state the values

4. **Family social history:**

Is there a family history of liver disease? **(Tick where appropriate)** YES ☐ NO ☐

History of alcohol intake **(tick where appropriate)** YES ☐ NO ☐

Brand of alcohol:

Bottled alcohol YES ☐ NO ☐

Number of bottles per week

Wine YES ☐ NO ☐

Number of wine glasses per week

Spirits YES ☐ NO ☐

Number of sachets per week

If yes, for how long **(Indicate the number)** Years ☐ Months ☐ Days ☐

Have you ever been in contact with someone with Hepatitis (yellow eyes)

YES ☐ NO ☐

Have you ever had a blood transfusion? YES ☐ NO ☐ Don't Know ☐

Sources of food:

Processed YES ☐ NO ☐

Maize YES ☐ NO ☐

Rice YES ☐ NO ☐

Groundnuts YES ☐ NO ☐

Milk and Milk products YES ☐ NO ☐

Storage methods and duration …….

Others:

5. **Clinical diagnosis:**

Hepatitis: YES ☐ NO ☐

Acute YES ☐ NO ☐

Chronic YES ☐ NO ☐

Secondary to: Hepatitis B virus YES ☐ NO ☐

Hepatitis C virus YES ☐ NO ☐

Liver Cirrhosis YES ☐ NO ☐

Hepatocellular carcinoma YES ☐ NO ☐

Others:

6. Ultrasound findings:

Liver cirrhosis: YES ☐ NO ☐

Liver lesions:

Solitary YES ☐ NO ☐

Multiple Indicate the number ……

Diffuse YES ☐ NO ☐

Echo pattern:

Homogenous YES ☐ NO ☐

If yes,

Hypoechoic YES ☐ NO ☐

Isoechoic YES ☐ NO ☐

Hyperechoic YES ☐ NO ☐

Heterogeneous YES ☐ NO ☐

Size:

0-1mm

1.1-3mm

> 3.1mm

Others

Ultrasound diagnosis:

……

…….

7. **CT scan findings:**

Enhancement pattern

Late arterial phase (35 Seconds):

Hyper attenuating (Vividly enhancing) YES ☐ NO ☐

Porto-venous phase:

Hypo-attenuating (early wash out) YES ☐ NO ☐

Delayed phase:

Iso-attenuating to the liver YES ☐ NO ☐

CT scan

diagnosis……

……

APPENDIX 2: DATA ANALYSIS TOOL

DUMMY TABLES

Table 1; Demographics (N=102)

	Frequency n (%)
Gender	
Male	
Female	
Age	
18-25	
26-35	
36-45	
46-55	
56-65	
>65	
Residence	
Makueni	
Nandi	
Nairobi	
Others	

Table 2: Laboratory results

	Frequency n (%)	
	Yes	**No**
HBsAg		
HCsAg		
Serum AFP		
Serum DCP		

Table 3; Chief complaints (N=102)

	Frequency n (%)	
	Yes	**No**
Yellow eyes		
Abdominal distension		

Table 4; Family social history (N=102)

	Frequency n (%)	
	Yes	**No**
Family history of liver disease		
History of alcohol intake		
Bottled		
Wine		
Spirit		
Contact with someone with Hepatitis		
Ever had a blood transfusion		
Processed food		
Maize		
Rice		
Groundnuts		
Milk and milk products		

Table 5; Clinical diagnosis (N=102)

	Frequency n (%)	
	Yes	**No**
Hepatitis		
Acute		
Chronic		
Secondary to: Hepatitis B virus		
Secondary to: Hepatitis C virus		
Liver Cirrhosis		
Hepatocellular carcinoma		

Table 6; Ultrasound findings (N=102)

	Frequency n (%)	
	Yes	**No**
Liver cirrhosis		
Liver lesions		

Table 7; Size of lesions (N=102)

	Frequency n (%)
0-1mm	
1.1-3mm	
> 3.1mm	

Table 8; Tri phasic CT scan attenuating findings (N=243)

	Frequency n (%)	
	Yes	**No**
Late arterial hyper attenuating		
Porto-venous hypo attenuating		
Delayed Iso-attenuating		

APPENDIX 3; ENGLISH CONSENT FORM FOR PARTICIPATION IN THE STUDY

Research title: Ultrasound imaging detection of hepatocellular suspicious lesion among high risk patients attending Kenyatta National Referral Hospital

This consent form consists of the following:

- Participant information sheet
- Consent form for signing
- Statement by the researcher/research assistant.

PARTICIPANT INFORMATION SHEET

Investigator's statement.

I am Dr Malindi Ephranzia Chao, a postgraduate student at the University of Nairobi, department of diagnostic imaging and radiation medicine. I am conducting a study on ultrasound imaging detection of hepatocellular suspicious lesion among high risk patients**.** Ultrasound and Triphasic CT scan will be used for the study. There are no radiations with ultrasound but there is radiation with CT scan. Therefore only those who will pick liver lesions on ultrasound will be subjected to CT scan for further evaluation of the lesions. You will be required to lie supine (on your back). No procedural pain will be experienced.

This consent form is to help you decide whether you want to be part of the study or not. It would be a pleasure if you are part of the study.

You are free to ask any questions before, during and after the study. Please read through the form.

Introduction

Hepatocellular carcinoma is a primary cancer of the liver. It's amongst the leading cause of high rates of cancer related mortality in the world and in the country. Its main risk factors is infectious cause from Hepatitis B virus and Hepatitis C virus, followed by non-infectious causes such as chronic alcohol intake and aflatoxins. The latter is fungal contamination of stored food.

Study purpose

Screening is recommended for early detection of HCC and management. In Kenya there is no standard protocol for HCC screening. Therefore the study will help in developing a protocol for screening all high risk patients in developing HCC.

Study Procedures

Each participant will undergo abdominal ultrasound using a curvilinear probe, while lying supine on an examining table. Those who the researcher picks a suspicious lesion will be further subjected to tri phasic CT scan imaging.

Benefits and risks

This study will provide a screening protocol that will help diagnostic radiologists in early detection of HCC lesion before it advances and timely intervention by gastroenterologist/ oncologist in managing patient.

HCC has a prolonged subclinical growth period during which curative treatment option are possible from surgical to chemotherapy hence the purpose of screening.

No risks will be encountered with ultrasound during the study, but for those with lesions will be subjected to CT scan which has some risks from radiation and contrast reaction from the contrast media which will be used for scanning. Possible benefits will include better visualization and characterization of the suspicious lesions.

There will be no extra cost to the participant for taking part in the study.

Duration of study

6 months.

Confidentiality

All information will be treated with confidentiality and any relevant medical information regarding the results and the data collected will be accessible to the researcher.

The information may be looked at by the supervisors where relevant to the study.

Information obtained will be kept under lock and key and soft copy information will be password protected. No specific information of any participant will be revealed to any person without their permission in writing. Your names/relatives names will not appear on any of the records used for this study.

Voluntariness of participation

Your participation in this study is voluntary and refusal or withdrawal from the study will not be denied treatment of any form. If you agree to take part you shall be required to sign the underlying consent form. You may withdraw from participating in the study at any time with no consequence whatsoever.

Compensation

There will be no compensation, financial or otherwise, will be offered to the participants. Neither will any preferential treatment, gift or reward, be awarded to the participants during or after the duration of the study.

Contact information

Should you require any further information or clarification regarding your participation in this study, please feel free to contact the following:

Principal researcher:

Dr. Malindi E. Chao,

Masters of Medicine resident in Diagnostic Imaging and Radiation Medicine,

Department of Diagnostic Imaging and Radiation Medicine,

University of Nairobi

P.O. Box 3266-00506 Nairobi

Email address: ephychao13@gmail.com

Cell phone number 0724-551-464,

For queries concerning your rights as a research participant you may contact the Kenyatta National Hospital- Ethics and Research Committee. It is the mandate of this committee to protect you, if you chose to participate, from harm.

University of Nairobi

College of Health Sciences

P.O Box 19676-00202

Tel. (254)0202726300 Ext 44355

Kenyatta National Hospital

P.O Box 20723-00202

Tel. (254)020 726300 Ext 44102, 44355

Fax: 725272

E-mail: uonknh erc@uonbi.ac.ke

PARTICIPANT CONSENT FORM AND PARTICIPANTS STATEMENT

I the undersigned hereby confirm that the doctor has explained to me about the above study and I understand fully. I have been given the opportunity to ask questions which have been adequately answered.

I understand that my participation is voluntary and that I have not been forced to participate. I understand that I can decline without giving any reason, without my medical care or legal rights being affected.

I understand that I will not receive any remuneration or preferential treatment, and will not receive any gift or reward, for participating in the above study.

I understand that my personal information will be kept confidential, but that any relevant medical information regarding the results of my scans and the data collected will be accessible to the researcher, and may be looked at by her supervisors where relevant to the study. I give them permission to have access to this information.

I hereby consent to my participation in this study.

Signed: …… (Patient)

Date: …….

Unique Patient ID: …….....

Signed: ……. (Witness)

STATEMENT BY RESEARCHER/RESEARCH ASSISTANT

I hereby confirm that I have accurately read out the contents of the information sheet to the participant.

To the best of my ability, I have made sure the participant understands the following;

Participation in this study is on voluntary basis and no compensation will be given.

Refusal to participate or withdraw from the study at any point will not in any way compromise the quality of care accorded to the patient.

All the information that shall be given will be treated with confidentiality.

Name: _____

Signature: _____

Date: _____

Respondent's Code ……

Date ……

APPENDIX 4: FOMU YA IDHINI YA KUSHIRIKI KATIKA UTAFITI

Fomu ya idhini ya kushiriki katika utafiti

Mada: Matumizi ya uchunguzi wa ultrasound katika kutambua uvimbe wa maini miongoni mwa wahusika walio katika hadhari ya kupata saratani ya maini katika Hospitali ya Taifa ya Kenyatta.

Fomu hii ina sehemu tatu:

- Maelezo kwa ufupi kuhusu utafiti
- Fomu ya kukubali kushiriki katika utafiti
- Thibitisho la mtafiti/mtafiti msaidizi

KAULI YA MTAFITI.

Jina langu ni Dr Malindi Ephranzia Chao mwanafunzi wa uzamili katika Chuo Kikuu cha Nairobi idara ya radiologia na dawa mionzi. Matumizi ya uchunguzi wa ultrasound katika kutambua uvimbe wa maini miongoni mwa wahusika walio katika hadhari ya kupata saratani.

Ultrasound itatumika katika utafiti. Hakuna mionzi wakati ultrasound inatumika walakini kwa CT scan iko, kwasabau hiyo ni wale watakao patikana na uvimbe wa maini pekee watakao fanya CT scan. Utapaswa kulala kwa mgongo (kulala chali). Hakuna uchungu utahisi wakati utaratibu unatendeka.

Madhumuni ya fomu hii ya idhini ni kukusaidia kuamua kama unataka kushiriki katika utafiti huu au la. Itakuwa ni furaha yangu ukishiriki katika hii utafiti.

Unao uhuru wa kuuliza maswali yoyote kabla, wakati wa na baada ya utafiti. Tafadhali soma fomu hii Kwa makini.

Maelezo kwa ufupi kuhusu utafiti

Utangulizi

Kutambua saratani ya maini mapema ikiwa bado haijaenea mwilini kutumia vipimo vya kutambua saratani ya maini ambavyo vinafahamika kwa lugha ya kitaalam kama ultrasound ni jambo la muhimu sana. CT scan inauwezo ya kuangalia sehemu nyembamba za maini kwa hivyo inaweza kutofautisha uvimbe tofauti za maini.

Madhumini ya utafiti

Utafiti huu utatumiwa kuunda protokoli yenye itatumiwa na madaktari kwa kutibu mgonjwa.

Utafiti haujafanywa kuhusu protokoli za kuonyesha saratani ya maini nchini Kenya. Utafiti huu utasaidia kuonyesha iwapo kuna ubora wa kutumia teknolojia ya ultrasound kama kifaa chifaacho kwa kuweza kuonyesha saratani ya maini. Kenya kama nchi pia tunafaa kuwa na mikakati ya kuweza kutambua saratani ya maini mapema iwezejanavyo.

Madhara na faida

Kuongeza uchunguzi wa CT scan kwa ultrasound kutasababisha kuongezeka kwa kipimo cha mionzi. Faida za uchunguzi huu ni uwezo wa kuonekana vizuri kwa uvimbe huu wa maini. Hakutakuwa na gharama ya ziada kwa mhusika.

Muda wa utafiti.

Miezi sita.

Utaratibu wa Mafunzo

Kila mshiriki atapata uchunguzi wa ultrasound. Na wale watapatika na uvimbe wata pimwa zaidi na CT scan.

Kujitolea kwa mshiriki

Kushiriki kwako katika utafiti huu ni kwa hiari yako. Ukiamua kutojiunga hauwezi kukataliwa huduma za matibabu yako hospitalini. Ukiamua kujiunga na utafiti huu, utapewa fomu hii ya maelezo na utatarajiwa kutia sahihi ya kukubali kushiriki katika utafiti huu. Una uhuru wa kujiondoa katika utafiti huu wakati wowote bila athari zozote.

Siri ya utafiti

Taarifa zote namatokeo ya utafiti huu zitalindwa vilivyo na kuwekwa katika hali ya siri. Hakuna taarifa maalum ya mshiriki yeyote zitafafanuliwa Kwa mtu yeyote bila ya idhini yako Kwa maandishi. Majina yako hayataonekana kwenye kumbukumbu za Utafiti huu.

Fidia

Hakutakuwa na fidia ya kifedha au vinginevyo kwa washiriki , hakuna upendeleo , zawadi au malipo.

Maelezo ya mawasiliano

Ukihitaji ufafanuzi zaidi kama mhusika kuhusu utafiti huu tafadhali uwe huru kuwasiliana na:

Mtafiti mkuu:

Dk. Malindi E. Chao,

Idara ya radiologia na dawa mionzi

Chuo Kikuu cha Nairobi

SLP 3266-00506 Nairobi

Email address: ephychao13@gmail.com

Nambari ya simu 0724-551-464,

Ukiwa na maswali yoyote kuhusu haki zako kama mshiriki katika utafiti huu unaweza wasiliana na KNH - UON Maadili na Kamati ya Utafiti. Ni jukumu la kamati hili kukulinda kutoka na madhara ukijchagua kushiriki katikia utafiti huu.

KNH-UoN-ERC secretariat

Katibu WA utafiti

Chuo Kikuu cha Nairobi-Hospital kudu ya Kenyatta

Sandusky la Posta 20723-00202 KNH

Nairobi.

Ambary ya same: 72600-9

Fax: 725272

Bara pepe: UoNknherc@uonbi.ac.ke

FOMU YA KUIDHINISHA KUSHIRIKI KATIKA UTAFITI

Mimi kwa hiari yangu mwenyewe natoa dhibitisho kwamba daktari amenieleza vikamilifu kuhusu utafiti ambao kichwa chake kimetajwa hapo juu. Ninakiri kuwa pia nimepewa fursa ya kuuliza maswali kuhusu utafiti huu na nimeridhika na majibu niliyopewa na daktari/mtafiti msaidizi.

Ninaelewa kwamba kushiriki katika utafiti huu ni kwa hiari yangu mwenyewe na sijalazimishwa.

Natambua kwamba sitapokea fidia yoyote iwe fedha au vinginevyo, wala sitapokea matibabu yoyote ya upendeleo, takrima au tuzo kwa ajili yakushiriki kwangu katika utafiti huu.

Naelewa kuwa taarifa zangu za kibinafsi zitakuwa siri. Ingawa hivyo taarifa kuhusu matokeo ya uchunguzi zitakazokusanywa wakatiwa utafiti huu zitaangaliwa na kuchambuliwa na mtafiti mkuu pamoja na wasimamizi wake pindi itakavyohitajika.

Ninatoa idhini yangu kushiriki katika utafiti huu.

Shashi..... (Mshiriki)

Tarehe.....

Ambary ya siri ya Mshiriki.....

Shashi: ..... (Shahidi)

DHIBITISHO LA MTAFITI/MTAFITI MSAIDIZI

Ninadhibitisha ya kuwa nimemwelezea mshiriki mambo yafuatayo kuhusu utafiti huu;

Kwamba kushiriki ni kwa hiari yake.

Hakuna fidia yoyote itakayopeanwa kwa kushiriki katika utafiti.

Mshiriki anaweza kubadili uamuzi wa kuendelea kushiriki katika utafiti huu bila ya kuadhiri huduma ya matibabu yake.

Haki za mshiriki zitalindwa na habari zitakazotolewa na mshiriki zitawekwa siri wakati wote na zitatumika kwa ajili ya utafiti huu pekee yake

Jina.....

Shashi.....

Tarehe.....

Ambary ya siri ya Mshiriki.....

Shashi: .....