

Assessment of Diagnostic Accuracy of Tri-phasic Computed Tomography in Differentiating Cirrhosis Nodules from Hepatocellular Carcinoma Nodules



SUPERIOR UNIVERSITY

**Thesis Submitted to
The Superior University Lahore
In Partial Fulfillment of the
Requirement for the Degree of
Master of Science in Allied Health Sciences**

By

AMMARA JABEEN

SU91-MSAHW-S23-017

Session: 2023-2025

Faculty of Allied Health Sciences

2023 - 2025

AMMARA JABEEN

SU91-MSAHW-S23-017

FAHS

**Assessment of Diagnostic Accuracy of Tri-phasic Computed
Tomography in Differentiating Cirrhosis Nodules from Hepatocellular
Carcinoma Nodules**



SUPERIOR UNIVERSITY

**Thesis Submitted to
The Superior University Lahore
In Partial Fulfillment of the
Requirement for the Degree of
Master of Science in Allied Health Sciences**

By

AMMARA JABEEN

SU91-MSAHW-S23-017

Session: 2023-2025

Faculty of Allied Health Sciences

Author's Declaration

I hereby state that my MS thesis titled “**Assessment of Diagnostic Accuracy of Tri-phasic Computed Tomography in Differentiating Cirrhosis Nodules from Hepatocellular Carcinoma Nodules**” is my work and has not been submitted previously by me for taking any degree from this University

The Superior University, Lahore,

or anywhere else in the country/world.

At any time if my statement is found to be incorrect even after my MS, the university has the right to withdraw my MS/M.Phil. degree.

Ammara Jabeen

Date: _____

Plagiarism Undertaking

I solemnly declare that research work presented in the thesis titled “**Assessment of Diagnostic Accuracy of Tri-phasic Computed Tomography in Differentiating Cirrhosis Nodules from Hepatocellular Carcinoma Nodules**” is solely my research work with no significant contribution from any other person.

Small contribution/help wherever taken has been duly acknowledged and that complete thesis has been written by me.

I understand the zero-tolerance policy of the HEC and University,

The Superior University, Lahore,

towards plagiarism. Therefore, I as an author of the above-titled thesis declare that no portion of my thesis has been plagiarized and any material used as a reference is properly referred/ cited. I undertake that if I am found guilty of any formal plagiarism in the above-titled thesis, even after awarding of MS/M.Phil. degree, the University reserves the rights to withdraw/revoke my MS/M.Phil. degree and that HEC and the University have the right to publish my name on the HEC/University website on which names of students are placed who submitted a plagiarized thesis.

Student/Author Signature: _____

Ammara Jabeen:

Research Completion Certificate

This is to certify that the thesis entitled “**Assessment of Diagnostic Accuracy of Tri-phasic Computed Tomography in Differentiating Cirrhosis Nodules from Hepatocellular Carcinoma Nodules**” submitted by “**Ammara Jabeen**” has been accepted towards the partial fulfillment of the requirement for “**MS Allied Health Sciences**”. The quality of the work contained in this thesis is adequate for the award of degree.

Signature: _____

Dr. Tahira Batool
Assistant Professor

Certificate of Approval

This is to certify that the research work presented in this thesis, titled **“Assessment of Diagnostic Accuracy of Tri-phasic Computed Tomography in Differentiating Cirrhosis Nodules from Hepatocellular Carcinoma Nodules”** was conducted by **“Ammara Jabeen”** under the supervision of **“Dr. Tahira Batool”**

No part of this thesis has been submitted anywhere else for any other degree. This thesis is submitted to the Faculty of Allied Health Sciences, The Superior University, Lahore in partial fulfillment of the requirements for the degree of Master of Science in the field of **“Allied Health Sciences”** in Faculty of Allied Health Sciences at The Superior University, Lahore.

Ammara Jabeen:

Signature: _____

Examination Committee:

Session Chair:

Signature: _____

a) External Examiner:

Signature: _____

b) Internal Examiner:

Signature: _____

c) Dr. Tahira Batool:

Signature: _____

d) PL/HOD: Dr. Hafiz Shehzad

Signature: _____

e) Dean: Prof. Dr. M. Naveed Babur

Signature: _____

f) Controller of Examination: Dr. M. Haris

Signature: _____

DEDICATION

Firstly I dedicate my work to Almighty Allah who is our creator and make me capable for doing this project. I also dedicate my work to my parents Mr. Muhammad Afzal and Mrs. Safia (late) who have always my backbone and taught me to never let down. I also dedicate my work to my teachers who guide me in this endeavored. In dedicate my work to my friends who always encouraged me to complete my research work. In the last I dedicate my work to worthy patients who gave me their personal medical record to fulfill my research work, without their cooperation and help this work cannot be reached to an end.

Ammara Jabeen

ACKNOWLEDGEMENT

In the name of Allah, the most Gracious, the most Merciful.

I am extremely thankful to Almighty ‘Allah’ who is the entire source of knowledge and wisdom endowed to mankind, for providing me with the acumen and vision to complete this endeavor.

I would like to express my profound gratitude to my supervisor Dr. Tahira Batool for her wise counsel and encouraging attitude towards this study. I am extremely grateful to him/her for immensely facilitating me during my study period by ensuring the provision of favorable circumstances and conducive environment. This project would not have been possible without his support and expert guidance.

In the end, I would like to extend my deepest gratitude to the patients who gave me their personal medical record to fulfill my research work and to my family members. Without their encouragement, I would not have been able to complete this endeavor.

Ammara Jabeen

TABLE OF CONTENTS

	Page
DEDICATION.....	v
ACKNOWLEDGEMENT.....	vi
TABLE OF CONTENTS	vii
LIST OF TABLES	viii
LIST OF FIGURES	ix
LIST OF ABBREVIATION.....	x
ABSTRACT.....	xi
CHAPTER 1-----	01
INTRODUCTION.....	01
OBJECTIVES.....	11
CHAPTER 2-----	12
LITERATURE REVIEW -----	12
CHAPTER 3-----	25
METHODOLOGY-----	25
3.1 Research design.....	25
3.2 Clinical settings.....	25
3.3 Sample size.....	25
3.4 Sampling technique.....	25
3.5 Duration of study.....	25
3.6 Selection criteria.....	25
3.6.1 Inclusion criteria.....	25
3.6.2 Exclusion criteria.....	25
3.7 Ethical consideration.....	26
3.8 Data collection procedure.....	26
3.9 Data analysis	26
CHAPTER 4-----	27
RESULTS-----	27
CHAPTER 5-----	32

DISCUSSION-----	32
CONCLUSION -----	38
REFERENCES.....	39
APPENDICES.....	xiii
Appendix- 1.....	xiii
Appendix- 2.....	xiv
Appendix- 3.....	xv

LIST OF TABLES

Table No.	Description	Page
Table 2.1	CT findings of Hepatocellular Carcinomas	21
Table 4.1	Density of cirrhotic nodules on CT	27
Table 4.2	Density of hepatocellular carcinoma nodules on CT	28
Table 4.3	Cross Tabulation of HCC nodules on CT	42
Table 4.4	Sensitivity & Specificity of HCC nodules on CT	42
Table 4.5	Cross Tabulation of Cirrhotic nodules on CT	43
Table 4.6	Sensitivity & Specificity of HCC nodules on CT	43
Table 4.7	Independent sample T-test of Density of cirrhotic nodules on CT	44
Table 4.8	Independent T-test of enhancement of cirrhosis nodules on CT	44
Table 4.9	Independent sample T-test of Density of Hepatocellular carcinoma nodules on CT	45
Table 4.10	Independent T-test of enhancement of Hepatocellular carcinoma nodules on CT	45

LIST OF FIGURES

Figure No.	Description	Page
Figure 4.1	ROC curve of enhancement of cirrhosis nodules on CT	27
Figure 4.2	ROC curve of enhancement of hepatocellular carcinoma nodules on CT	28

LIST OF ABBREVIATIONS

DAA	Direct-acting antiviral
SVR	Sustained virologic response
CTAP	Computed tomography arterio- portography
VEGFR-2	Vascular endothelial growth receptor-2
MRI	Magnetic Resonance Imaging
PET	Positron Emission Tomography
HCC	Hepatocellular Carcinoma
DN	Degenerating Nodules
CEUS	Contrast Enhanced Ultrasonography
HCC	Hepatocellular carcinoma
US	Ultrasound
HBsAg	Hepatitis B surface Antigen

ABSTRACT

Background: Hepatocellular carcinoma is basically a type of tumor originating from liver cells. A condition called cirrhosis causes the liver to become permanently damaged and scarred. Computed Tomography (CT) scan is best for identifying and evaluating hepatic cancers. When contrast material is injected, multiphasic scanning with helical CT improves hepatocellular carcinoma detection and staging.

Objective: The aim of this study was to assess the diagnostic accuracy of tri-phasic computed tomography in differentiating between cirrhotic nodules and hepatocellular carcinoma nodules.

Methodology: This was a cross-sectional study design. It was carried out in Arif Memorial Teaching Hospital. Non-probability convenient Sampling technique was used. Statistical analysis was conducted using SPSS version 26.0, with Receiver Operating Curve (ROC) to assess the diagnostic accuracy of tri-phasic CT for differentiating both nodules. Independent sample t-test was also applied.

Results: Initial finding of area under curve (AUC) for a ROC curve value of 0.4 and independent sample t-test shows a 0.01 p-value for cirrhotic nodules while for hepatocellular carcinoma nodules area under curve for a ROC curve shows a value of 0.9 and independent sample t-test shows a value of 0.8. Our study showed that sensitivity of CT for cirrhosis nodules was 63% and specificity was 90% and for HCC nodules sensitivity was 90% and specificity was 20%.

Conclusion: In conclusion tri-phasic computed tomography has good diagnostic accuracy for hepatocellular carcinoma nodules as compared to cirrhotic nodules.

Key words: Computed Tomography, Hepatocellular carcinoma, Cirrhotic Nodules Sensitivity, Specificity.

Chapter 1

INTRODUCTION

The most frequent primary hepatic tumor, hepatocellular carcinoma (HCC) ranks sixth globally in terms of frequency of occurrence and can cause up to one million deaths yearly. The incidence of discovering HCC by computed tomography (CT) has grown from 1.4 to 2.4 per 100,000 over the past 20 years, and this has resulted in a 41% increase in the overall death rate (1). However, the ability to distinguish between benign and malignant nodules using noninvasive imaging techniques is restricted and is mostly dependent on the differences in their vascular supplies. Regenerative nodules have a portal venous blood supply, similar to the underlying liver parenchyma, but high-grade degenerating nodules and HCC show signs of *de novo* arteriogenesis, as seen by a rise in non-tri- radial or unpaired arteries (2). Less than 5% of patients with symptomatic, untreated HCC survive after five years. On the other hand, 80% of patients with cirrhosis who have had a tiny (2 cm) HCC transplanted survive for five years. It is obvious that a tiny HCC's discovery is essential to the patient's outcome (1).

It can be challenging to distinguish HCC morphologically from other hepatic nodules. There are several benign regenerative nodules present in cirrhotic livers. Pathologic evaluation frequently allows for the histological differentiation of premalignant dysplastic nodules (DN) and small HCC from background cirrhotic regenerative nodules with bi-cellular atypia and stromal micro-invasion (2).

The pathology and imaging results in the livers of people who receive transplants differ from those of patients who do not in a number of ways. Explanted livers from patients with viral or alcoholic cirrhosis tend to reveal a more advanced disease state than those reported in Asia from partial hepatectomy specimens. This is due to the fact that only Child patients may withstand a lengthy hepatic resection, but the majority of patients undergoing orthotopic liver transplantation are frequently Child class C patients (3). To our knowledge, there has never been any documentation of the specifics. There is some controversy surrounding the report in one series that all enhancing lesions observed in patients with liver cirrhosis were actually hepatocellular carcinoma.

However, there are anecdotal reports of enhancing lesions in patients with cirrhosis coming from a variety of causes, including hypo vascular lesions that mimic hepatocellular carcinoma (4). Furthermore, Asian hematopathologists identified DN (formerly known as adenomatous hyperplasia) from hepatectomy materials considerably earlier than transplant facilities in the United States and Europe; these centers didn't start reporting these lesions until the early to mid-1990s. early computed tomography research from North America (3).

Cirrhotic liver is one of the trickier radiological cases. It is challenging to identify significant underlying problems because of the damaged and twisted liver architecture. The fact that these patients have a significantly higher risk of developing hepatocellular carcinoma exacerbates the issue. Not only are these tumors hard to find in cirrhosis patients, but the disease itself can produce lesions that resemble tumors. Owing largely to arterial phase enhancement's improved capacity to detect early, tiny lesions, contrast-enhanced helical CT has emerged as the most widely utilized screening modality for hepatocellular carcinoma in cirrhosis patients while it is well known that the sensitivity of helical CT and contrast-enhanced MR imaging to detect hepatocellular carcinoma in cirrhosis patients ranges from 50% to 70% (4).

CT techniques are best for identifying and evaluating hepatic cancers. When contrast material is injected, multiphasic scanning with helical CT improves hepatocellular carcinoma detection and staging. However, because the gold standard for the diagnosis of hepatocellular carcinoma or other nodules is typically based on either the findings at partial hepatic resection or clinical and imaging studies with or without biopsy, it is impossible to ascertain the true sensitivity and specificity of multiphasic helical CT. Pathologic investigation frequently finds incidental hepatocellular carcinomas, particularly tiny ones, that were overlooked by imaging techniques. In this sense, pathologic analysis of the removed liver should be done before determining the actual sensitivity of an imaging test (4, 5).

Cirrhosis is the term describing the histological development of regenerative nodules surrounded by fibrous bands as a result of chronic liver injury. End-stage liver disease and portal hypertension are brought on by this illness. Recent advancements in our knowledge of the etiology, natural history, and treatment of its effects have improved

the management, quality of life, and life expectancy of people with cirrhosis. The main subjects of this lecture will be the diagnosis, implications, and treatment of cirrhosis along with contemporary developments in science and practice (5).

Cirrhosis, the 14th most common cause of death globally and the fourth most common cause of death in central Europe, is increasingly common in more developed countries as a source of morbidity and mortality. The idea that cirrhosis is not a single condition, but rather a disease that may be classified into various clinical prognostic stages is gaining traction. Precaution should be the new paradigm in the management of patients in order to stabilize the disease's course (6).

It is commonly recognized that, regardless of the cause of liver illness, cirrhosis is the most powerful risk factor for the onset of hepatocellular carcinoma. The occurrence of HCC in different liver disorders, particularly liver cirrhosis (LC), has not yet been precisely compared, though. Furthermore, it is currently unknown how much cirrhosis increases in a variety of liver illnesses. In this study, we conducted a meta-analysis to compare the incidence of HCC in LC in different liver illnesses. We also examined the ways in which the occurrence of developing HCC in the cirrhotic condition is rising in comparison to the non-cirrhotic state in different liver disorders. We also go over potential pathways for HCC formation in a variety of liver conditions (7).

Any liver lesion outside of the normal parenchyma, regardless of whether it results in structural or functional abnormalities of the hepatic-biliary system, is called as a liver nodule. These lesions can be changed in size. Both benign and malignant tumors are possible. Regional and ethnic variations are evident in the prevalence of different liver pathologies. In Europe and the US, a liver nodule is more likely to be a metastatic deposit than a primary malignancy; however, with a prevalence of 8–10%, hepatocellular carcinoma ranks as the fourth most prevalent liver disease in Pakistan. When compared to data from the West, this prevalence rate is considerable (8).

The most common primary liver tumor and the leading cause of death for people with cirrhosis is hepatocellular carcinoma (HCC). In the cirrhotic population, the yearly incidence of HCC ranges from 3% to 5%. A poor prognosis (0%–10% 5-year survival) is linked to a diagnosis made after symptoms appear and when the tumor stage is already advanced. However, early diagnosis of HCC can lead to effective treatments and long-

term life (50% to 70% 5-year survival) (21).

Hepatocellular carcinoma (HCC) has been found early enough to enable curative treatment by follow-up surveillance of cirrhosis patients. A method for differentiating HCCs from other hepatic lesions smaller than 3 cm that are found during ultrasonography (US) screening of the livers in patients with cirrhosis is outlined in the practice recommendations of the American Association for the Study of Liver Diseases. According to the guidelines, nodules larger than 1 cm in diameter should be further examined using magnetic resonance imaging (MRI) or dynamic contrast material-enhanced computed tomography (CT). Therefore, treating the nodule as though it were HCC may be justified if arterial hyper-vascularization is found. For hypo vascular nodules, defined as lesions that look less enhanced than the surrounding liver both on arterial and venous phase images (22).

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related deaths and the sixth most common type of cancer globally. HCC is the primary cause of death for patients with liver cirrhosis, which is complicated by HCC in over 90% of cases. The only way to ensure long-term survival is to diagnose the tumor early when appropriate therapy may be applied, as the rate of HCC at 5 years may surpass 25%. As a result, all guidelines advise screening for HCC in cirrhosis patients who would receive treatment if they were found to have the disease. Ultrasound (US) is used for screening, and a significant clinical difficulty is the unambiguous diagnosis of a US-detected nodule within a cirrhotic liver. Confirmation by biopsy has many drawbacks. Ascites, coagulation issues, and tumor location may make needle insertion impossible, and there are dangers involved (bleeding or seeding) (23).

The accurate identification of a nodular lesion, discovered by imaging modalities in a liver with cirrhosis, remains a crucial problem for clinicians. The issue is particularly complicated for small (1-3 cm) nodules, because many of these may be pre neoplastic lesions with uncertain malignant potential,¹ such as macro regenerative nodules, low-grade dysplastic nodules (LGDN) or high-grade dysplastic nodules (HGDN), or more rarely, hemangiomas , which can be found altogether in up to 42% of cases in explanted livers. The choice of whether to treat these nodules is crucial since it is acknowledged that some of them may have little foci of hepatocellular carcinoma (HCC) and that the

majority will develop into HCC over a few years. Arterial hyper vascularization, detected at contrast-enhanced imaging techniques, is now regarded as a distinctive feature of HCC in cirrhosis, because non neoplastic nodules still have a prevalent portal vascularization. This feature was taken into account in the European Association for the Study of the Liver (EASL) document for the clinical management of HCC, where confirmation of the arterial hyper vascular pattern by two imaging techniques, even in the absence of a significant (400 ng/mL) rise in α -fetoprotein, was suggested as diagnostic criteria for HCC in nodules larger than 2 cm in patients with cirrhosis, whereas histological confirmation plays a pivotal role in the diagnosis of nodules of 1 to 2 cm because of the potential inaccuracy of imaging techniques in such small nodules (24).

An excess of recurrent HCC was originally reported by Reign and co-workers in patients with a previous HCC who underwent antiviral therapy with DAAs (27.6% in 5.7 months from the beginning of antiviral treatment), while a study by Cardoso and collaborators reported an unexpectedly high risk of de novo HCC in patients with SVR following antiviral therapy (7.4% during a mean follow-up of 12 months) in a strict time-dependent relationship between treatment with DAA and HCC onset. These results sparked concerns that premalignant liver nodules or clinically undetectable clones of HCC might quickly develop into detectable HCC due to either a DAA-mediated increase in vascular endothelial growth factor (VEGF), as suggested by a recent prospective study, or a rapid removal of HCV with DAA, which is thought to impact immune surveillance against cancer. This may also be the takeaway from a multicenter trial conducted in the United States, which found that patients treated with DAA experienced a shorter period between tumor eradication and return than individuals who were not treated for any number of reasons. Nonetheless, the majority of these studies' shortcomings include their retrospective design and the enrollment of patients whose primary goal was to receive SVR, with little data collected related to the risk of developing HCC (25).

Recent developments in imaging techniques have made it easier to identify tiny hepatocellular carcinomas (HCCs), and the prognosis of these lesions has significantly improved (1). In individuals with liver cirrhosis or chronic hepatitis, small HCCs are

typically found using computed tomography (CT) or periodic ultrasonography (US). Nonetheless, a number of different kinds of hepatocyte nodular lesions can be seen on US or CT scans. These include regenerative nodules, adenomatous hyperplasia (AH), which is also known as adenomatous hyperplastic nodule, adenomatous hyperplasia, or macro regenerative nodule, atypical AH, which are lesions that fall somewhere between benignity and malignancy, and AH with malignant foci. Their US and CT characteristics are strikingly similar to those of small HCCs. Consequently, it is now crucial to distinguish these lesions from little HCCs. However, we previously discovered that while portal blood flow exists in these lesions, CT during arterial portography (CTAP), which is used for the accurate diagnosis and preoperative assessment of hepatic tumors, typically does not clearly show regenerating nodules and areas of arterial enhancement (26).

Architectural distortion and the formation of a variety of nodules, from benign regenerative nodules to dysplastic nodules to openly malignant hepatocellular carcinoma (HCC), are hallmarks of cirrhosis, a gradual widespread process of liver fibrosis. Over the past 20 years, the frequency of HCC in North America has nearly doubled, and the prognosis is not good. The best treatment for HCC is resection or transplantation, which significantly improves survival when detected early. In one study, patients with minimal illness had an 85% 4-year recurrence-free survival rate after liver transplantation. Because cadaveric organs are scarce, it is crucial to identify nodules containing HCC early on in order to control tumor burden while waiting for transplantation and to identify patients who may benefit from transplantation in the long run versus those who won't (27).

Although the clinical significance of macro nodules detected "in vivo" and their management are still up for debate and the subject of much research, the majority of the studies addressing their natural outcome were retrospective or primarily limited to large regenerative or atypical/border-line lesions. The differential diagnosis of small nodular lesions arising in cirrhosis is essentially limited to early hepatocellular carcinoma (HCC) and non-malignant macro nodules, which include large regenerative, low, and high grade dysplastic nodules. Up until now, the general consensus is that high grade dysplastic nodules are the true precursors of HCC, while the remaining nodules are

thought to be only marginally involved in human liver carcinogenesis. Some factors predicting the malignant transformation of 32 ultrasonography detected hepatocellular nodules have surfaced in a recent study, however the results were deemed tentative due to the small cohort size (28).

Nodular hepatic lesions, also known as adenomatous (adenomatous) hyperplasia (AH), have received a lot of attention lately since they may be precancerous lesions for HCC. Unfortunately, there is no established terminology or unambiguous definition for these lesions. AH currently refers to both nodular liver lesions with cytological and structural atypical and those without such alterations. Previously, we divided nodular lesions in cirrhotic livers into two prototypes: a large regenerative nodule and a dysplastic nodule (borderline lesion), excluding overt HCC nodules. While the latter exhibits various atypical alterations that histologically mimic HCC, the former nearly exhibits the same histological structure as typical pseudo lobules in a cirrhotic liver. Determining whether a simple big regenerative nodule develops into HCC through the dysplastic nodule is crucial. In this work, we tracked changes in histological features and clinical courses over time to assess the precancerous potentiality of large regenerative nodule (29).

One of the last common pathways of many chronic liver illnesses is liver cirrhosis, which is characterized by regenerative nodules (RNs) of the hepatic parenchyma encircled by fibrotic bands. One it is commonly accepted that hepatocytes proliferate locally and become trapped by extracellular matrix deposition to become RNs. Numerous attempts have been attempted to determine the location of registered nurses, frequently by looking at females' X-chromosome-linked markers. For instance, in hepatitis C virus-induced liver cirrhosis, restriction fragment length polymorphism of the X-chromosome-linked phosphor glycerol kinase gene and random methylation-induced gene inactivation have revealed that almost half of all RNs are monoclonal. Studying the pattern of inactivation of the X-linked human androgen receptor gene (HUMARA) revealed a similar outcome, with monoclonal RNs accounting for 45% of cases.⁴ Nevertheless, the location of X-inactivated cells in the liver is not considered in either of these investigations. The offspring of a single X- inactivated embryonic cell may be grouped together since X-inactivation (L- yonization) happens really early in embryogenesis. "Patches" are collections of cells that have a common X-inactivation

pattern; in the human colon, these patches can span up to 400 crypts. A RN that appears in the center of a patch in the liver would therefore be mono phenotypic for an X-linked marker, though it might be derived either mono clonally or poly clonally (30).

The pre-malignant potentiality of large regenerative nodules (LRNs) and dysplastic nodules (DNs) remains contentious despite the publication of numerous follow-up studies on these nodules. In our earlier investigation, no LRNs exhibited malignant transformation; nonetheless, some writers claimed that LRNs were pre-malignant. However, because there was not yet broad agreement on the histological criteria for well-differentiated hepatocellular carcinoma (HCC), DN, and LRN, these older data are difficult to compare. Furthermore, the follow-up periods were shorter and there were fewer nodules overall. Some reports looked at more than 90 nodules, while others looked at less than 40. The longest follow-up period was shorter than five years in four out of the nine earlier investigations. If the numbers of nodules and the lengths of the follow-up periods had been greater, the results might also have been different (31).

An international panel of experts classified the various types of benign and malignant hepatocellular nodules that have been described, all of which are caused by previous hepatic injury, based on two main sets of criteria: (a) whether the hepatic cells are regenerative or dysplastic, and (b) the anatomic characteristics of the adjacent hepatic stoma. Making this distinction is crucial because the clinical implications range from completely benign (e.g., focal nodular hyperplasia) to blatantly malignant, with other nodules of intermediate concern. Budd-Chiari syndrome and other systemic illnesses that cause vascular derangement of the liver may have big (multiacinar) regenerative nodules among the benign nodules. Combining the resources of several institutions has allowed us to investigate a significant number of patients with these lesions, and we believe that, in the majority of cases, a precise diagnosis may be made based on clinical correlation and characteristic imaging findings. The pathologic-imaging connection, clinical characteristics, and differential diagnosis of large liver regenerating nodules are covered in this article (32).

CTAP is the preferred method of preoperative work-up of candidates for hepatic surgery, especially for the detection of small hepatic tumors like hepatocellular carcinoma (HCC) and metastatic tumors, because it is the most sensitive modality in the

depiction of small liver lesions. Since CTHA can be used in conjunction with CTAP and seems to be more useful when used in conjunction with CTAP, it can show hypervascular hepatic tumors or even hypo-vascular metastases. Abnormal nodules like HCC or dysplastic nodules often stand out against the background of cirrhotic liver parenchyma at CTAP and CTHA. Portal hypertension and Porto systemic shunt frequently because reduced or reversed portal flow in patients with severe cirrhosis. CTAP is typically nonspecific, showing false-positive perfusion abnormalities or benign diseases such hemangiomas and cysts. According to Peterson et al., regenerating nodules were the most often seen benign nodular lesions at CTAP. It is challenging to interpret CTAP investigations because lower attenuation nodules or the mottled appearance of hepatic parenchyma brought on by regenerative nodules and fibrosis mimic neoplasms (33).

Hepatocellular carcinoma (HCC) is the second leading cause of cancer death and the fifth most prevalent type of cancer globally. According to estimates, 80% of HCCs in cirrhosis patients arise through a multi-step carcinogenesis process that starts with a regenerative nodule (RN), progresses to a dysplastic nodule (DN), and ends with HCC. Because more therapeutic choices are available when a possible malignancy is identified early, post-treatment recurrence rates are reduced and long-term survival is improved. Accurately differentiating between RN, DN, and tiny HCC is crucial for efficient treatment. For newly discovered nodules during HCC surveillance, recent practical guidelines suggest using contrast-enhanced CT, MRI, or contrast-enhanced ultrasonography (CEUS) as a logical next step. To assess the liver nodules in terms of various enhancing patterns, a variety of imaging features were employed. CEUS is better at identifying nodule hyper-vascularity because of real-time assessment than CT or MRI, which may not show arterial phase hyper-enhancement (APHE) because of arterial phase mistiming. As a result, CEUS may be useful in describing non-hyper vascular, unidentified lesions on CT and MRI. Furthermore, CEUS has benefits such as low cost, simplicity of use, and non-radioactivity, making it a useful tool for HCC surveillance (34).

Hepatic venous outflow obstruction, regardless of the mechanism or degree of obstruction, is known as Budd-Chiari syndrome (BCS). From tiny hepatic veins to the

inferior vena cava's (IVC) right atrium entry, this blockage can be seen. This definition does not include hepatic outflow obstruction linked to sinusoidal obstruction syndrome (SOS), right heart failure, or pericardial disease since they are distinct pathophysiological and clinical entities. Hepatic venous occlusion is the most frequent cause of primary BCS in the Western world, and it typically affects women. In Asian populations, however, it is typically idiopathic or linked to structural abnormalities such membranous blockage. It frequently affects men and is brought on by blockage of the hepatic vena cava. Hepatocyte necrosis, atrophy, and severe centrilobular congestion are all brought on by BCS. Consequently, a few weeks following venous blockage, parenchymal fibrosis appears. As the disease progresses, regenerative nodules may form from hepatic atrophy and increasing fibrosis. These nodules typically have a perioral distribution, are numerous, hyper-vascularized, and dispersed throughout the liver. This outcome leads to a rise in portal hypertension and portal branch compression (35).

AIM AND OBJECTIVE

To assess the diagnostic accuracy of tri-phasic computed tomography in differentiating cirrhosis nodules and hepatocellular carcinoma nodules.

Chapter 2

LITERATURE REVIEW

Velázquez et al (9) conducted a study in 2017; he revealed that elements linked to the development of hepatocellular carcinoma (HCC) may enhance the effectiveness of surveillance initiatives. A program of early diagnosis includes 463 individuals with liver cirrhosis in Child class A or B, ranging in age from 40 to 65. We assessed the prediction power of several risk factors with the Cox regression model and the Kaplan-Meier method. HCC struck thirty-eight patients. Upon doing a multivariate analysis, four characteristics emerged as independent predictors of the development of hepatitis C virus (HCC): anti-HCV antibody positive, age 55 years or older, pro thrombin activity 75% or less and less platelet count. Based on how much each of these components contributed final model.

SG, et al (10) in 2010, discovered that it is widely known that liver cirrhosis of various etiologies is associated with an increased risk of developing HCC. The incidence of HCC in different liver disorders has not yet been compared, though. We conducted a survey on this comparison. We searched the PubMed database from 1989 to 2017 for English-language publications that reported on the development of HCC in various liver disorders based on prospective follow-up outcomes. A meta-analysis was carried out for every liver condition. The following are the annual incidence(%) of HCC in the cirrhotic and non-cirrhotic stages as well as the ratio of HCC incidence in the cirrhotic stage to the non-cirrhotic stage. The liver illnesses are caused by the hepatitis B and C viruses.

Tarao et al (11) in 2019, revealed that in tropical Africa and south-east Asia, hepatocellular carcinoma is still very common and is primarily associated with chronic hepatitis B virus infection. Although primary prevention, which involves immunizing newborns at or near birth, is effective, millions of people continue to be chronically infected, thus any reduction in the frequency of tumors cannot be predicted for decades, even in nations where the resources are available. As a result of the widespread use in recent years, chronic hepatitis C virus infection has been on the rise

in Japan, the USA, and the Mediterranean countries of Europe, the Middle East, and North Africa. Molecular biology research on hepatic carcinogenesis implicating the hepatitis B virus gene has yielded a wealth of information.

Sasaki et al (12) in 2017 discovered that in patients with liver cirrhosis, hepatic carcinogenesis is thought to be a primary cause of postoperative recurrence of de novo hepatocellular carcinoma (HCC). According to reports, the degree of underlying liver impairment and the results of HCC surgery are connected. It is still unknown, though, how frequently postoperative de novo HCC recurs and how often it does so annually. Precancerous lesions, particularly adenomatous/dysplastic nodules and large-cell/small-cell changes, are still hotly debated topics. It's also not quite clear how to distinguish nodular lesions in cirrhosis from early-stage carcinoma. It is uncommon for hepatocellular carcinoma to spontaneously resolve. It is most likely immune mediated, and after surgery, therapy with activated T-lymphocytes may lower the recurrence rate. The diagnosis of hepatocellular carcinoma in challenging cases has been made considerably easier by the positive identification of the disease by a liver-specific antibody.

Tsai et al (13) in 2019, investigated 102 cirrhotic HCC patients, with non-hepatic disease controls participated in a case-control study to determine whether hepatitis B virus and hepatitis C virus (HCV) infection are risk factors for liver cirrhosis and hepatocellular carcinoma. In comparison to controls (16.6%, 10.5%), the prevalence's of hepatitis B surface antigen and antibody to HCV were greater in HCC and liver cirrhosis. Anti-HCV was more common in cirrhotic HCC (66.6%) and liver cirrhosis (46.1%) in HBsAg-negative patients than in controls. Patients that tested positive for HBsAg did not show this difference. Both HBsAg and anti-HCV were significant risk factors for HCC, according to multivariate analysis (odds ratio).

Colombo et.al (14) in 2021 indicated that over follow-up periods average 33 months hepatocellular carcinoma was discovered in 29 patients at baseline and in 30 patients of 417 patients who were tumor-free at baseline. Patients with continuously elevated serum alpha-fetoprotein levels had a higher cumulative risk of developing hepatocellular carcinoma during follow-up than did patients with levels or those with

consistently normal levels. Only 17 patients had tumors that might be removed. Among those found during follow-up, the percentage of possibly operable tumors was significantly lower than the percentage at enrollment.

Brancatei et al (15) in 2015 revealed in his study that a single-detector helical CT screening was performed on 1329 cirrhosis patients who were recommended for transplant recovery. The patients were monitored for 19 months or until transplantation after undergoing one or more helical CT exams over a 30-month period. With infusion rates of 2.5–5.0 mL/sec, we mostly employed un-enhanced and biphasic contrast-enhanced approaches. A total of 435 patients had transplants throughout this time (15).

Bolond et al (16) in 2023 showed a study in which liver specimens were sectioned and each lesion's histologic confirmation was directly compared to the pathology and imaging results. For the primary data analysis, prospective preoperative helical CT reports were utilized. A retrospective, un-blinded examination was conducted to identify the features of lesions that were mistakenly identified as hepatocellular carcinoma.

Nayak et al (17) in 2019 in his retrospectively study, assessed a contrast-enhanced CT dataset of 40 patients with three subject groups: healthy patient 14, cirrhosis 12 patients, and cirrhosis with HCC 14 patients. A unique approach was created and compared with the most advanced deep learning-based technology for the automatic 3D segmentation of liver utilizing modified region- growing segmentation technique.

Martino et al (18) in 2014 showed that, using logistic regression, histogram parameters were determined from segmented CT liver volume to distinguish between livers that were healthy and pathological (cirrhosis and HCC). Support vector machines were used in a multi-phase CT image analysis process to extract 24 temporal variables for the purpose of diagnosing liver HCC and cirrhosis.

Singa et al (19) in 2018 revealed that, 145,396 patients with HCC in 59 trials that we found, 41,052 (28.2%) had surveillance-detected HCC. After correcting for lead-time bias, HCC surveillance was linked to better early-stage identification, receiving curative therapy, and overall survival; yet, there was significant variability in all pooled

estimates. Across studies, the percentage of patients who suffered bodily injury associated to monitoring varied from 8.8% to 27.5%, with the majority of these injuries being moderate in nature.

Tüysüz et al (35) in 2024 suggested that Budd-Chiari syndrome (BCS), regenerative nodules may form from hepatic atrophy and increasing fibrosis due to decreased portal and venous outflow and hyper-arterialization. We used contrast-enhanced CT to assess the frequency and detection rate of hepatocellular carcinoma, as well as the imaging properties of regenerative hepatic nodules, their incidence rates in diagnosis and follow-up, and the yields of the CT scan technique validated by pathological examination. Thirty-three liver transplant recipients with primary chronic BCS were included in this two-center retrospective analysis. A multiphase procedure was employed to acquire images throughout the arterial, portal-venous, and delayed phases prior to and following the application of contrast. Images from three-dimensional tomography and CT angiography were acquired. The main conclusion was the balance between the pathological and CT imaging findings. Relationships between nodule incidence rate in BCS and nodule malignancy development rate, as well as between nodule and HCC development and blood type and disease duration, were secondary outcomes. Computed tomography demonstrated a sensitivity of 78.3%, a positive predictive value of 90.0%, a specificity of 80.0%, and a negative predictive value of 61.5% in identifying the nodules that were pathologically identified.

Kim et al (36) in 2016 investigated that A rapid reduction in portal and arterial blood flow, followed by ischemic necrosis, is the cause of infarcted regenerative nodules in patients with liver cirrhosis. Although these lesions are uncommon in stable patients, they commonly appear in those who have recently experienced gastrointestinal bleeding, mainly from variceal hemorrhage. It might be difficult to distinguish these lesions from other localized lesions, such as metastases and hypovascular hepatocellular carcinomas (HCCs).. Laboratory tests showed the following results: hemoglobin, 10.4 g/dL; hematocrit, 31.8%; white blood cell count, 4,230/ μ L; and platelet count, 69,000/mm³. The blood chemistry profile was as follows: total protein, 5.5 g/dL; albumin, 3.1 g/dL; total bilirubin, 0.7 mg/dL; aspartate aminotransferase (AST), 45 U/L; and alanine aminotransferase (ALT) 31 U/L. His pro-thrombin time (14.4 seconds) and international

normalized ratio (1.31) were prolonged.

Thaiss et al (37) in 2016 investigated case of HCC in a patient with cirrhosis and a history of variceal hemorrhage that could not be differentiated from many infarcted regenerating nodules. A 70-year-old man with alcoholic cirrhosis went to the ER due to dizziness and discomfort in his epigastrium. Four years ago, he was diagnosed with a 1.3-cm single nodular HCC, and following three sessions of trans-arterial chemoembolization (TACE) with doxorubicin, he had a full response. His baseline resting heart rate was 45 to 55 beats per minute, and his pulse rate was 72 beats per minute when he arrived. His blood pressure was 63/45 mmHg. Since VEGFR-2 expression influences prognosis and treatment options, it is important to determine whether VEGFR-2-expression in hepatocellular carcinoma (HCC), dysplastic (DLN), and regenerative liver nodules (RLN) correlates with pre-histology, in vivo Dynamic Contrast Enhanced-Computerized Tomography (DCE-CT) data.

Nagasue et al (38) in 2018 estimated that ten individuals with "hepatocellular pseudo tumor in the cirrhotic liver" (regenerating hyper-plastic nodule) in the last six years. All of the patients were men between the ages of 40 and 82. Seven of them drank alcohol regularly. Seven had either anti-HBs or anti-HBc, but none tested positive for HBs-Ag. Six individuals who did not have hepatocellular carcinoma at the time of the pseudo tumor diagnosis had serum AFP levels ranging from 4 to 28 ng/ml. Seven cases had ultrasonography, two had computed tomography, and one had angiography to show the lesions. In each of the five cases examined, the liver scan came out negative. Three patients had pre-operative diagnoses of hepatocellular carcinoma, three had pseudo tumor in the cirrhotic liver, and one had recurrent carcinoma, all of which were confirmed or highly suspected. Pseudo-tumor was inadvertently found in excised tissues of hepatocellular carcinoma in three further patients. Seven individuals had synchronous or meta chromos development of cancer, according to the histological and follow-up investigations. It has yet to be determined whether these cirrhotic liver lesions are premalignant.

Choi et al (39) in 2013 investigated that chronic liver illness is one of the most significant elements in carcinogenesis, hepatocellular carcinomas often arise in conjunction with liver cirrhosis. Recent reports of pathologic investigations of resected

specimens from cirrhotic livers indicate small nodular lesions (i.e., regenerating nodule, adenomatous hyperplasia, and early hepatocellular carcinoma) that are related with small hepatocellular carcinomas (less than 3 cm in diameter). A regenerating nodule may represent the initial stage of hepatocellular carcinoma in the cirrhotic liver's hepatic carcinogenesis, which progresses in stages of adenomatous hyperplasia and early hepatocellular carcinoma. We examine the current understanding of the role of these related lesions in carcinogenesis and detail the pathologic features of small hepatocellular carcinomas and accompanying nodular hepatic lesions. Additionally, we go over the imaging results of these anomalies, the effectiveness of different imaging methods in identifying them, and the significance of imaging in treatment planning (39). Kanematsu et al (40) in 2003 estimated that 32 tiny hepatic nodules were seen by sonography and verified pathologically in 23 consecutive cirrhotic patients suspected of having HCC. Six lesions required definitive surgery, and 26 were verified by ultrasonographically guided aspiration needle-core biopsy. Records of ultrasound exams were examined in the past. Two radiologists conducted a blind retrospective examination of CT and MR images acquired using different imaging modalities (40). Elsayes et al (41) in 2017 investigated that interpretation of liver imaging results in patients who are at risk for hepatocellular carcinoma (HCC), the Liver Imaging Reporting and Data System (LI-RADS) was developed. A committee of diagnostic radiologists with experience in liver imaging, backed by the American College of Radiology, worked together and continuously to establish this approach. Hepatic biliary surgeons, hepatic logists, hepatic pathologists, and interventional radiologists all provided invaluable input. This article reviews the 2017 edition of LI-RADS for magnetic resonance imaging and computed tomography. The right population for LI-RADS application, technical guidelines for image optimization, such as definitions of dynamic enhancement phases, diagnostic and treatment response categories, major and ancillary imaging feature definitions, criteria for differentiating definite HCC from a potentially non-HCC malignancy, management options after LI-RADS categorization, and reporting are some specific topics.

Sangiovanni et al (25) in 2020 suggested that De novo HCC occurred in 48 patients (annual incidence 3.1/100 patient-years, 75% BCLC 0-A) and recurred in 40 patients

(mean yearly incidence 29.9/100 patient-years, 83% BCLC 0-A) throughout a median study period of 17 months in group 1 and 16 months in group 2. In patients with UNMNs in group 1, the HCC immediate incidence peaked at 4.2 months, while in group 2, it peaked at 7.7 months. Multivariable Cox regression models showed that the incidence of de novo HCC was independently associated with UNMNs (hazard ratio [HR] 3.11; 95% CI 1.47–6.57; $p = 0.003$), ascites detected at any time prior to enrollment (HR 3.04; 95% CI 1.23–7.51; $p = 0.02$), and alpha-fetoprotein log-value (HR 1.90; 95% CI 1.05–3.44; $p = 0.03$), while alcohol abuse history (HR 2.10; 95% CI 1.08–4.09; $p = 0.03$) and history of HCC recurrence (HR 2.87; 95% CI 1.35–6.09; $p = 0.006$) were associated with HCC recurrence.

Matsui et al (26) in 2015 investigated that using a variety of imaging techniques, the blood supply of nodular lesions linked to liver cirrhosis were examined in vivo. Computed tomography (CT) was used to assess the portal blood supply during arterial portography (CTAP); hepatic angiography, CT angiography, CT after intra-arterial injection of iodized oil, or ultrasound after intra-arterial injection of carbon dioxide micro-bubbles were used to assess the arterial blood supply. The study included 25 areas of adenomatous hyperplasia (AH) and 84 surgically confirmed hepatocellular carcinomas (HCCs) that were less than or equal to 3 cm. Only 6% of HCCs and 96% of AH patients at CTAP had a portal blood supply (chi 2, P less than .005). On the other hand, only 4% of AH cases and 94% of HCCs had an arterial supply larger than the surrounding liver (chi 2, P less than .005). Areas of AH with atypical hepatocytes and well-differentiated HCCs (Edmondson grade 1) tended to have blood supplies that were in the middle of those of arterial enhancement without atypia and those of HCC that were Edmondson and Steiner grade 2 or higher. In order to differentiate and treat early-stage HCC, it is thought to be helpful to assess the blood supply of the nodular lesions linked to liver cirrhosis.

Lin et al (30) in 2010 investigated that mutation in mitochondrial DNA (mt DNA) as indicators of clonal expansion to examine the clonality and cells of origin of regenerating nodules in human liver cirrhosis. Using histo-chemical and immune histo-chemical techniques, mutant cells are characterized phenotypically by a lack of the cytochrome c oxidase (CCO) enzyme, which is fully encoded by mtDNA. Of the 526

nodules from 10 cases, 18% were uniformly CCO-deficient, while just 3% had a mixed phenotype. Nodules were categorized as either CCO-positive or CCO-deficient. Hepatocytes were laser-capture micro dissected from multiple locations within distinct CCO-deficient nodules from frozen sections. Polymerase chain reaction sequencing of the complete mtDNA genome revealed mutations. The nodules were monoclonal in character in all but one instance, with each nodule containing up to four common mutations in all of its hepatocytes. Furthermore, the discovery of similar mutations in hepatic progenitor cells next to nodules deficient in CCO indicates that nodules may originate from these cells.

Duan et al (47) in 2020 estimated that mean age of the 149 patients (113 men and 36 women) with 162 FLLs was 53.4 ± 12.7 years. The probabilities of having a higher nodule ranking (RN < DN < small HCC) increased by 68% for every unit decrease in CATR (OR, 0.32; 95% CI, 0.20–0.50, $p < .001$). A higher nodule rating was adversely correlated with arterial phase hypo enhancement and iso-enhancement as opposed to hyper enhancement. Lower probabilities of a higher nodule ranking were linked to late-phase iso-enhancement. Comparing the CEUS + CATR model (Δ CH 0.92, 0.89–0.95) to the CATR model (Δ CH 0.09, 0.04–0.13, $p < .001$) and the CEUS model (Δ CH 0.03, 0.01–0.05, $p = .02$), the former demonstrated superior discriminatory capacity (34). Barrau et.al in 2016 assessed the sensitivity and specificity for a noninvasive diagnosis of HCC or high grade degenerative nodules using a single imaging technology (i.e., CT or MRI), as recently recommended by the 2016 updated AASLD recommendations. According to the findings, sensitivity varied from 75% to 79%, with MRI having the highest sensitivity, as other people have also noted. It's interesting to note that we had 100% specificity for either HGDN or HCC using any one imaging modality. Two distinct diagnostic approaches are used when the initial imaging modality is unable to produce a definitive diagnosis. We also assessed the sensitivity and specificity for a noninvasive diagnosis of HCC or HGDN using a single imaging technology (i.e., CT or MRI), as recently recommended by the 2016 updated AASLD recommendations. According to our findings, sensitivity varied from 75% to 79%, with MRI having the highest sensitivity, as other people have also noted. It's interesting to note that we had 100% specificity for either HGDN or HCC using any one imaging modality. Two

distinct diagnostic approaches are used when the initial imaging modality is unable to produce a definitive diagnosis.

Takayasu et al (48) in 2020 False-negative readings in CT are caused by partial-volume averaging and respiratory movement. HCCs might not be enhanced by contrast material in angiography. To ascertain operability and the most effective operational technique, more diagnostic tests are required. High sensitivity was demonstrated by lipiodol CT and portal angiographic CT in detecting tiny HCC lesions. Lipiodol CT outperformed sonography and CT for lesions smaller than 1 cm. To find lesions smaller than 1 cm, lipiodol CT is advised following angiography. Even though lipiodol CT was positive in one instance when the uptake of lipiodol was identified within the lesions, we obtained a false-negative result. Lipiodol was not retained within a 3-cm HCC lesion in this patient, and the lesion appeared hypovascular on angiography. Small lesions can also be seen on portal angiographic CT, albeit there was no discernible difference between lipiodol and portal angio-graphic CT. For comparison, more prospectively investigated instances are needed. Out of all the other imaging techniques, intraoperative sonography showed the highest sensitivity. It found all but two of the preoperatively indicated lesions. The results might have also been impacted by the typical three-month lag between preoperative imaging and intraoperative sonography. Sometimes intraoperative sonography is unable to identify HCC lesions smaller than 1 cm when the entire liver is made up of macro regenerative nodules.

Takayasu et al (54) in 2005 estimated that Nine (24%) of 37 lesions on unenhanced CT scans, 12 (31%) of 39 lesions on early enhanced CT scans (two had high density and one had low density [Fig. 1]), 20 (51%) of 39 lesions on late enhanced CT scans, and 22 (56%) of 39 lesions overall were found to have early hepatocellular carcinoma (Table 1).According to tumor size, CT had the following sensitivity for early hepatocellular carcinoma detection. Six (75%) of eight lesions were between 2 and 3 cm, 14 (61%) of 23 lesions were between 1 and 2 cm, two (29%) of seven lesions were no larger than 1 cm in diameter, and zero of one was between 3 and 4 cm, according to CT scans. CT has a higher detection rate for bigger tumors. In the left superior lateral lobe of the liver, directly beneath the heart, there was a single, sizable lesion (3.8 cm) that was invisible.

Table 2.1: CT findings in 39 early hepatocellular carcinomas in relation to tumor size (54).

Tumor size in cm	No.of lesion	Unenhanced CT			Contrast enhanced CT						No of lesion detected by combined CT
					Early Phase			Late phase			
		low	iso	high	low	iso	high	low	iso	high	
<1	7	1	6	0	1	6	0	2	5	0	2
1-2	23	4	17	0	6	15	2	12	11	0	14
2-3	8	4	4	0	3	5	0	6	2	0	6
3-4	1	0	1	0	0	1	0	0	1	0	0
total	39	9	28	0	10	27	2	20	20	0	22

Forner et al (49) in 2008 suggested the accuracy of dynamic magnetic resonance imaging (MRI) and contrast-enhanced ultrasound (CEUS) in diagnosing nodules 20 mm or smaller found during ultrasound (US) surveillance is evaluated prospectively in one research. A small single nodule (mean diameter, 14 mm) was found by US in 89 individuals with cirrhosis [median age, 65 years; male 53, hepatitis C virus 68, Child-Pugh A] who had no history of hepatocellular carcinoma (HCC). Baseline tests included hepatic MRI, CEUS, and fine-needle biopsy (gold standard) (FNB). CEUS at 3 months and MRI at 6 months were used to track non-HCC cases (median 23 months). FNB was carried out up to three times and whenever a change in aspect or size was detected. The delayed/venous phase's intense arterial contrast uptake and subsequent washout were recorded as conclusive for HCC. The final diagnoses were cholangiocarcinoma (n = 1), HCC (n = 60), and benign lesions (n = 28) such as focal nodular hyperplasia, hemangioma, and regenerative/dysplastic nodule. Alpha-fetoprotein (AFP) levels, liver function, cirrhosis etiology, and sex were comparable between the HCC and nonHCC groups. Patients with HCC had considerably bigger nodules and were older ($P < 0.0001$). Of 60 HCC patients, 42 had positive results from their initial biopsy. The

definitive profile's sensitivity, specificity, and positive and negative predictive values were 51.7%, 93.1%, 93.9%, and 50.9% for CEUS and 61.7%, 96.6%, 97.4%, and 54.9% for MRI. In both methods, the coincidental conclusive findings had values of 33.3%, 100%, 100%, and 42% (49).

Lee et al (50) in 2015 suggested that MR imaging is more sensitive per lesion and has a similar sensitivity per patient than CT for diagnosing hepatocellular carcinoma in patients with chronic liver disease. It also demonstrated a significantly higher sensitivity for lesions smaller than 1 cm, lesions in explanted livers, and all lesions when geodetic acid was used. There were 40 investigations total 6 on multi detector CT, 22 on MR imaging, and twelve on combined CT and MR imaging. The studies assessed 2489 patients with MR imaging and 1135 patients with multi-detector CT. MR imaging's overall per-patient sensitivity was 88% (95% CI: 83%, 92%), while its specificity was 94% (95% CI: 85%, 98%). When pooling the paired data from the 11 available trials, the overall per-lesion sensitivity of MR imaging was higher than that of multi-detector CT (80% vs. 68%, $P = .0023$). Compared to MR imaging using conventional contrast agents, geodetic acid-enhanced MR imaging demonstrated noticeably greater per-lesion sensitivity (87% vs. 74%, $P = .03$). Compared to HCCs 1 cm or larger ($P < .001$ for CT, $P = .02$ for MR imaging) and those in explanted livers ($P = .04$ for CT, $P < .001$ for MR imaging), per-lesion sensitivity was significantly lower for HCCs less than 1 cm (50).

Kudo et al (51) in 2008 found that With the exception of portal hypertension symptoms on US, there were statistically significant differences between LC and CH in the five imaging parameters assessed by CT, MRI, and US ($p < 0.001$). According to multivariate analysis, liver parenchymal abnormalities, portal hypertension symptoms, and liver morphological changes were the best predictive indicators for cirrhosis on MRI and CT, while irregular or nodular surfaces, blunt edges, or liver morphological changes were chosen as the best predictive indicators for cirrhosis on US. The greatest predictive indicators were 71.9, 77.1, and 67.6% by CT; 67.9, 67.5, and 68.3% by MRI; and 66.0, 38.4 (lower than CT and MRI, $p = 0.001$) and 88.8% (higher than CT and MRI, $p = 0.001$) by US. These results indicate the predictive diagnostic accuracy, sensitivity, and specificity in differentiating LC from CH. Diagnostic accuracy, sensitivity, and specificity were 67.0, 84.3, and 52.9% by CT; 70.3, 86.7, and 53.9% by MRI; and 64.0,

52.4 (lower than CT and MRI, $p = 0.0001$) and 73.5% (higher than CT and MRI, $p < 0.003$) by US, as determined by the imaging impression rating system. MRI and CT were marginally better than US in diagnosing LC, according to ROC analysis, but there was no statistically significant difference between the two. Cirrhosis was identified in 59.5, 46.7, and 41.7% of P-LC patients by US, CT, and MRI, respectively, with no discernible variation between these techniques for the pathological diagnosis of P-LC (51).

Nam et al (52) in 2011 revealed that 225 (35%) of the 638 patients had HCC, as determined by liver explant pathological investigation. The lesions were extensively multifocal or infiltrative in 23 of the cases. The corresponding lesion-based sensitivities of US, CT, and MRI in the remaining 202 explants (337 numerable, distinct nodules) were 46%, 65%, and 72% overall, and 21%, 40%, and 47% for small (<2 cm) HCC. The presence of CT or MRI data improved the sensitivity of US ($P = .049$); sensitivity values for lesions 2–4 cm and ≥ 4 cm were 62% and 85%, respectively. US, CT, and MRI patient-based specificities were 96%, 96%, and 87%, respectively.

Nadarevic et al (53) in 2021 estimated that With 21 studies and 3101 people overall, we included them. Because of the characteristics of the patients who were on waiting lists for orthotopic liver transplantation, we rated 86% (18/21) of the studies as having high worry and 14% (3/21) as having low concern with regard to applicability in the patient selection area. CT has a sensitivity of 77.5% (95% CI 70.9% to 82.9%) and a specificity of 91.3% (95% CI 86.5% to 94.5%) for hepatocellular carcinoma of any size and stage (21 studies, 3101 participants; low-certainty evidence). The sensitivity and specificity of CT for hepatocellular carcinoma were 71.4% (95% CI 60.3% to 80.4%) and 92.0% (95% CI 86.3% to 95.5%), respectively, according to 10 investigations with 1854 participants with low-certainty data.

Kudo et al (19) in 2008 suggested in a multicenter investigation that three radiologists with expertise in CT, MRI, and US blindly assessed the CT, MRI, and US scans of 142 patients with chronic liver disease who had surgery for complex hepatocellular carcinoma (less than 3 cm in diameter) in 10 institutions. Using a severity scale, the pictures were assessed for five imaging parameters: liver morphological changes, liver parenchymal abnormalities, blunt liver edge, uneven or nodular liver surface, and signs

of portal hypertension. Additionally, the diagnostic imaging impression score was computed. Three pathologists independently examined the resected liver specimens and histologically divided the patients into three categories: pre-cirrhosis (P-LC; n = 17), liver cirrhosis (LC; n = 71), and chronic hepatitis (CH; n = 54). To find independent predictive indicators of cirrhosis, a multivariate analysis (stepwise forward logistic regression analysis) was conducted by comparing the outcomes of the three imaging techniques with those from histology diagnoses. A receiver-operating characteristic (ROC) curve analysis was also used to assess the diagnostic efficacies of CT, MRI, and US for LC and early cirrhosis. The greatest predictive indicators were 71.9, 77.1, and 67.6% by CT; 67.9, 67.5, and 68.3% by MRI; and 66.0, 38.4 (lower than CT and MRI, $p = 0.001$) and 88.8% (higher than CT and MRI, $p = 0.001$) by US. These results indicate the predictive diagnostic accuracy, sensitivity, and specificity in differentiating LC from CH. Diagnostic accuracy, sensitivity, and specificity were 67.0, 84.3, and 52.9% by CT; 70.3, 86.7, and 53.9% by MRI; and 64.0, 52.4 (lower than CT and MRI, $p = 0.0001$) and 73.5% (higher than CT and MRI, $p < 0.003$) by US, as determined by the imaging impression rating system.

Chapter 3

METHODOLOGY

3.1 Research Design:

This was a cross-sectional study design.

3.2 Clinical Setting:

I was carried my study in Arif Memorial teaching Hospital.

3.3 Sample Size:

$$\text{Sample Size} = \frac{Z^2 \cdot P(1-P)}{d^2}$$

$$1-\alpha = 95$$

$$P = 80\% \quad d = 7\%$$

$$\text{Sample Size} = 126$$

3.4 Sampling Technique:

Non-probability convenient Sampling technique was used.

3.5 Duration of study:

The duration of my study was 8 months.

3.6 Selection Criteria:

3.6.1 Inclusion Criteria:

We were enrolled those patients in our study that were come in radiology department for CTscan with cirrhosis.

We were also enrolled those patients in our study that were come in radiology department for CT scan with hepatocellular carcinoma.

3.6.2 Exclusion Criteria:

We were excluded those patients in our study who were come in radiology department for CT scan other than cirrhotic and hepatocellular carcinoma disease.

We were also excluded those patients in our study that were come in radiology department for CT scan for biliary track, portal vein and hepatic artery diseases.

3.7 Ethical Consideration:

Synopsis entitled as "Assessment of diagnostic accuracy of triphasic computed tomography in differentiating cirrhosis nodules from hepatocellular carcinoma nodules" submitted by: Ammara Jabeen, Roll No. SU91-MSAHW-S23-017 had been approved for research work.

3.8 Data Collection Procedure:

The data was collected through questionnaire and CT scans. After taking the consent form, they were enrolled in the study.

3.9 Data Analysis:

The data was entered and analyzed by using the statistical package SPSS (version 26). Quantitative data were presented as Mean and Standard Deviation while percentage and frequency were calculated through SPSS. Data was interpreted in the form of graphs and tables. Receiver operating characteristic curve was applied to measure the diagnostic accuracy of computed tomography for both HCC nodules and cirrhosis nodules. Independent t-test was also applied to see the significance value of HCC nodules and cirrhosis nodules.

Chapter 4

RESULTS

In general Area under Curve (AUC) has value ranges from 0-1 for Receiver Operating Curve (ROC) curve. A value of 0.5 represents 50% of probability for correctly ranking random positive and negative examples. A value of 0.7 represents 70% of probability which means positive and negative with rank the positive is higher than the negative. A value of 0.8 and 0.9 represent excellent positive results.

According to my study results, AUC of a ROC curve analysis shows 0.4 value (less than 0.5) for cirrhotic nodules which means a true negative value while AUC for HCC nodules shows a value of 0.9 which means a true positive results.

In this study an Independent t- test is also applied. Out of 63 patients with cirrhotic nodules 33 patients have density and enhancement of cirrhotic nodules on CT while 30 patients don't have density and enhancement. Std. deviation of 33 is 0.478 while the other 30 patients have std. Deviation of 0.406 while out of 63 patients 54 patients have density and enhancement of HCC nodules on CT while 9 patients don't have density and enhancement. Mean and std. deviation of 21 samples are 2.90 and 0.30 respectively while the other 9 patients have mean and std. Deviation of 2.11 and 0.33 respectively.

According to my study AUC has value of 0.4 for Cirrhotic nodules and 0.9 value for HCC nodules which means cirrhotic nodules have true negative results while HCC nodules have true positive or excellent results on ROC curve. ROC curve represents that CT scan distinguished the HCC nodules better than the cirrhotic nodules.

In this study Lenene test shows the significance value of 0.019 and degree of freedom is 61. The t-test for equality of means shows the significance value of 0.120 and 0.241. The confidence interval is 95% (0.05) for cirrhotic nodules while the significance value of 0.80 for HCC nodules and degree of freedom is 28. The t-test for equality of means shows the significance value of <0.001 and <0.001. The confidence interval is 95% (0.05). This study shows that the P. value is significance for HCC nodules while not significant for cirrhotic nodules.

In this study 126 patient data was used which were divided into 2 groups. Both groups have 63 patients. Group 1 has cirrhotic nodules while group 2 has HCC nodules.

Results showed that 33 patients of group 1 have density on CT while 30 patients don't showed density on CT. Results of group 2 showed that 42 patients have density on CT while 21 patients don't have density on CT.

Table 4.1: Shows that total of 63 patients were presented with cirrhotic nodules on CT.

Density of cirrhotic nodules on CT	Frequency
Positive	33
Negative	30
Missing	0
Total	63

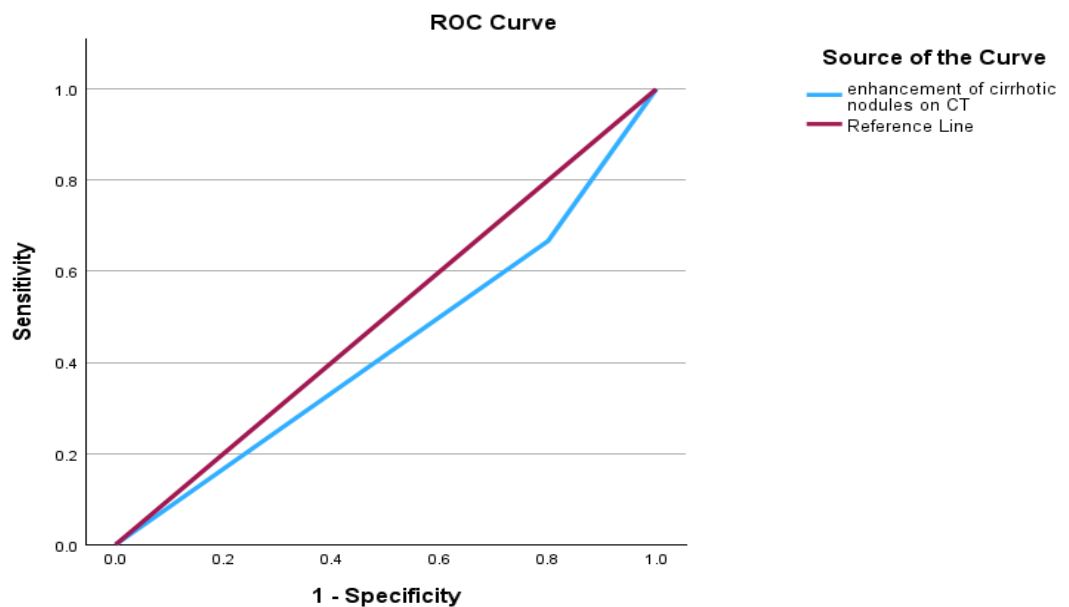


Figure 4.1: A ROC curve is drawn to see the diagnostic accuracy of tri-phasic CT. Blue line shows the enhancement of cirrhotic nodules on CT while red line is reference line. Area under the curve is 0.433.

Table 4.2: Shows that total of 63 patients were presented with HCC nodules on CT.

Density of HCC nodules on CT	Frequency
Positive	42
Negative	21
Missing	0
Total	63

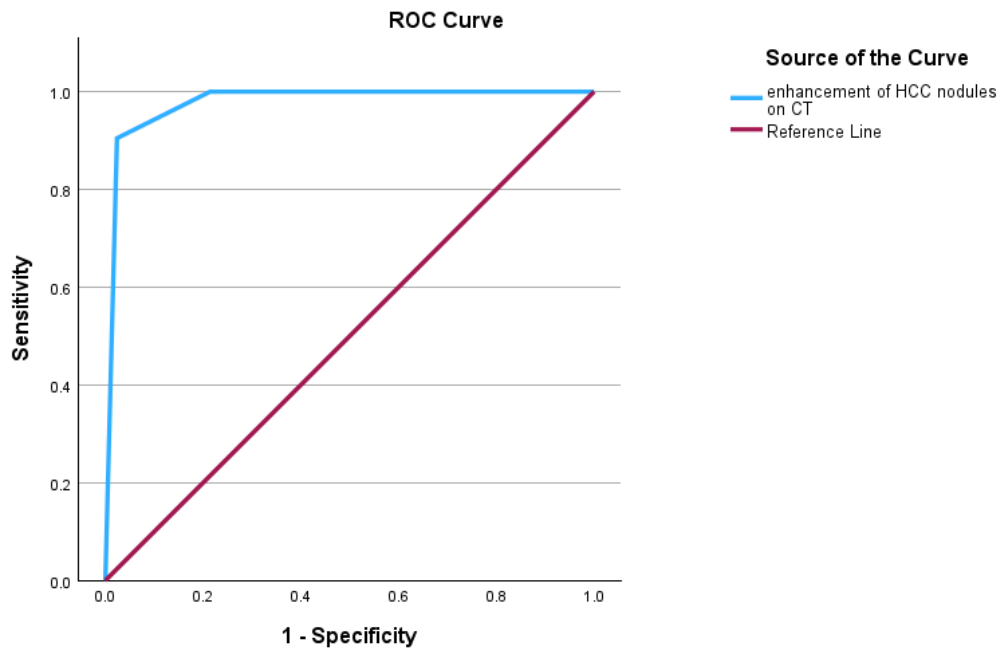


Figure 4.2: A ROC curve is drawn to see the diagnostic accuracy of tri-phasic CT. Blue line shows the enhancement of HCC nodules on CT while red line is reference line. Area under the curve is 0.97.

Table 4.3: Shows that total of 63 patients were presented with HCC nodules on CT.

	Cases					
	Valid		Missing		Total	
	N	Percentage	N	Percentage	N	Percentage
Test Results* Reality	63	100	0	0.0	63	100

Table 4.4: Shows Cross tabulation for HCC Nodules. Sensitivity was 85.71% & specificity was 71.42%.

Test Results* Reality Cross tabulation				
Test Result	Positive	Positive	Negative	Total
		36	06	42
	Count % within reality	85.71%	14.28%	66.67%
	Negative	03	18	21
		14.28%	71.42%	33.33%
Total				63 100%

Table 4.5: Shows that total of 63 patients were presented with cirrhotic nodules on CT

	Cases					
	Valid		Missing		Total	
	N	Percentage	N	Percentage	N	Percentage
Test Results* Reality	60	100	0	0.0	60	100

Table 4.6: Shows Cross tabulation for Cirrhosis Nodules. Sensitivity was 77.9% & specificity was 76.7%.

Test Results* Reality Cross tabulation				
Test Result	Positive	Positive	Negative	Total
		26	07	33
	Count % within reality	77.9%	27.3%	52.4%
	Negative	07	23	30
		23.28%	76.7%	47.6 %
Total				60 100%

Table 4.7: Shows the independent samples t- test. Out of 63 patients 33 patients have density 30 patients don't have density and enhancement.

Enhancement of cirrhotic nodules on CT	Density of cirrhotic nodules on CT	Frequency	Mean	Std. Deviation	Std. Error Mean
	present	33	1.6667	.47871	.08333
	absent	30	1.8000	.40684	.07428

Table 4.8: Levene test for equality of variance and t-test for equality of means for cirrhosis nodules.

Enhancement of cirrhotic nodules on CT		Levene Test for Equality of Variances				t-test for Equality of Means				95% Confidence Interval of the Difference	
						Significance					
		F	Sig	t	df	One Side p	Two Side p	Mean Difference	Std. Error Difference	Lower	Upper
	Equal Variances assumed	5.8	.01	-1.1	61	.12	.24	-.133	.11	-.35	.09
	Equal variances not assumed			-1.1	60.7	.11	.23	-.133	.11	-.35	.08

Table 4.9: Shows the independent samples t- test. Out of 63 patients 54 patients have density and enhancement of HCC nodules on CT while 9 patients don't have density and enhancement.

Enhancement of HCC nodules on CT	Density of HCC nodules on CT	Frequency	Mean	Std. Deviation	Std. Error Mean
	present	54	2.90	.300	.06
	absent	9	2.11	.33	.11

Table 4.10: Levene test for equality of variance and t-test for equality of means for HCC nodules.

enhancement of HCC nodules on CT		Levene Test for Equality of Variance s				t-test for Equality of Means				95% Confidence Interval of the Difference	
						Significance					
		F	Sig	t	df	One Side d p	Tw o- Side d p	Me an Diff ere nce	Std. Erro r Diffe renc e	Lowe r	Upper
	Equal varian ce assum es	.6	.80	6.41	28	<.00	<.00	.79	.12	.54	1.04
Equal varian c not assum es			6.1	13.8	<.00	<.00	.79	.12	.51	1.07	

Chapter 5

DISCUSSION

Based on this study, CT techniques is best for identifying and evaluating hepatic cancers. When contrast material is injected, multiphasic scanning with helical CT improves hepatocellular carcinoma detection and staging (4, 5). Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related deaths and the sixth most common type of cancer globally. HCC is the primary cause of death for patients with liver cirrhosis, which is complicated by HCC in over 90% of cases (23). According to a study it is widely known that liver cirrhosis of various etiologies is associated with an increased risk of developing HCC (10). Another study discovered that in patients with liver cirrhosis, hepatic carcinogenesis is thought to be a primary cause of postoperative recurrence of de novo hepatocellular carcinoma (12).

According to a study investigated, there were 40 investigations total 6 on multi detector CT, 22 on MR imaging, and twelve on combined CT and MR imaging. The studies assessed 2489 patients with MR imaging and 1135 patients with multi-detector CT. MR imaging's overall per-patient sensitivity was 88% (95% CI: 83%, 92%), while its specificity was 94% (95% CI: 85%, 98%). When pooling the paired data from the 11 available trials, the overall per-lesion sensitivity of MR imaging was higher than that of multi-detector CT (80% vs. 68%, $P = .0023$). Compared to HCCs 1 cm or larger ($P < .001$ for CT, $P = .02$ for MR imaging) and those in explanted livers ($P = .04$ for CT, $P < .001$ for MR imaging), per-lesion sensitivity was significantly lower for HCCs less than 1 cm. According to my study sensitivity of CT for hepatocellular carcinoma nodules was 90% while specificity was 20% (50).

In another study conducted in found that With the exception of portal hypertension symptoms on US, there were statistically significant differences between LC and CH in the five imaging parameters assessed by CT, MRI, and US ($p < 0.001$). According to multivariate analysis, liver parenchymal abnormalities, portal hypertension symptoms, and liver morphological changes were the best predictive indicators for cirrhosis on MRI and CT, while irregular or nodular surfaces, blunt edges, or liver morphological changes were chosen as the best predictive indicators for cirrhosis on US. The greatest predictive indicators were 71.9, 77.1, and 67.6% by CT; 67.9, 67.5, and 68.3% by MRI; and 66.0,

38.4 (lower than CT and MRI, $p = 0.001$) and 88.8% (higher than CT and MRI, $p = 0.001$) by US. These results indicate the predictive diagnostic accuracy, sensitivity, and specificity in differentiating LC from CH. Diagnostic accuracy, sensitivity, and specificity were 67.0, 84.3, and 52.9% by CT; 70.3, 86.7, and 53.9% by MRI; and 64.0, 52.4 (lower than CT and MRI, $p = 0.0001$) and 73.5% (higher than CT and MRI, $p < 0.003$) by US, as determined by the imaging impression rating system. While our study showed that sensitivity of CT for cirrhosis nodules was 63% and specificity was 90% and for HCC nodules sensitivity was 90% and specificity was 20% (51).

Another study showed that the corresponding lesion-based sensitivities of US, CT, and MRI in the remaining 202 explants (337 numerable, distinct nodules) were 46%, 65%, and 72% overall, and 21%, 40%, and 47% for small (<2 cm) HCC. The presence of CT or MRI data improved the sensitivity of US ($P = .049$); sensitivity values for lesions 2–4 cm and ≥ 4 cm were 62% and 85%, respectively. US, CT, and MRI patient-based specificities were 96%, 96%, and 87%, respectively. While our study showed that sensitivity of CT for cirrhosis nodules was 63% and specificity was 90% and for HCC nodules sensitivity was 90% and specificity was 20% (52).

According to another study three pathologists independently examined the resected liver specimens and histologically divided the patients into three categories: pre-cirrhosis (P-LC; $n = 17$), liver cirrhosis (LC; $n = 71$), and chronic hepatitis (CH; $n = 54$). To find independent predictive indicators of cirrhosis, a multivariate analysis (stepwise forward logistic regression analysis) was conducted by comparing the outcomes of the three imaging techniques with those from histology diagnoses. A receiver-operating characteristic (ROC) curve analysis was also used to assess the diagnostic efficacies of CT, MRI, and US for LC and early cirrhosis. Diagnostic accuracy, sensitivity, and specificity were 67.0, 84.3, and 52.9% by CT; 70.3, 86.7, and 53.9% by MRI; and 64.0, 52.4 (lower than CT and MRI, $p = 0.0001$) and 73.5% (higher than CT and MRI, $p < 0.003$) by US, as determined by the imaging impression rating system. According to our study sensitivity of cirrhosis lesion was 63% while specificity was 90% (19).

CT has a sensitivity of 77.5% (95% CI 70.9% to 82.9%) and a specificity of 91.3% (95% CI 86.5% to 94.5%) for hepatocellular carcinoma of any size and stage (21 studies, 3101 participants; low-certainty evidence). The sensitivity and specificity of CT

for hepatocellular carcinoma were 71.4% (95% CI 60.3% to 80.4%) and 92.0% (95% CI 86.3% to 95.5%), respectively, while according to our study it was 90% and 20%. (53). The Receiver Operating Curve (ROC) curve's Area under Curve (AUC) typically has a value between 0 and 1. The likelihood of accurately classifying random positive and negative instances is 50% when the value is 0.5. 70% of the likelihood is represented by a value of 0.7, meaning that the positive is greater than the negative. Excellent positive results are represented by values of 0.8 and 0.9 (25).

Based on the findings of my research, the AUC of a ROC curve analysis for cirrhotic nodules is 0.4 (less than 0.5), indicating a true negative result, whereas the AUC for HCC nodules is 0.9, indicating a true positive result.

An independent t-test is also used in this investigation. 30 individuals do not show density and enhancement of cirrhotic nodules on CT, but 30 of the 63 patients with cirrhotic nodules do. Of the 30 patients, 33 had a standard deviation of 0.478. 54 of the 63 patients had density and enhancement of HCC nodules on CT, compared to 9 who did not, resulting in a deviation of 0.406. Nine patients had mean and standard deviation, whereas 21 samples had mean and standard deviation of 2.90 and 0.30, respectively. 2.11 and 0.33 deviations, respectively.

A retrospectively study, assessed a contrast-enhanced CT dataset of 40 patients with three subject groups: healthy patient 14, cirrhosis 12 patients, and cirrhosis with HCC 14 patients. A unique approach was created and compared with the most advanced deep learning-based technology for the automatic 3D segmentation of liver utilizing modified region- growing segmentation technique. This study shows that CT is a good modality for picking up the HCC nodules (17).

According to my research, the AUC for cirrhotic nodules is 0.4, and for HCC nodules, it is 0.9. This indicates that cirrhotic nodules have true negative results on the ROC curve, whereas HCC nodules have real positive or great results. The ROC curve shows that the HCC nodules were more easily identified from the cirrhotic nodules by the CT scan.

In this study Lenene test shows the significance value of 0.019 and degree of freedom is 61. The t-test for equality of means shows the significance value of 0.120 and 0.241. The confidence interval is 95% (0.05) for cirrhotic nodules while the significance value of 0.80 for HCC nodules and degree of freedom is 28. The t-test for equality of means

shows the significance value of <0.001 and <0.001 . The confidence interval is 95% (0.05). This study shows that the P. value is significant for HCC nodules while not significant for cirrhotic nodules (17).

Two groups of 126 patients' data were used in this investigation. There are 63 patients in each group. While group 2 has HCC nodules, group 1 has cirrhotic nodules. According to the results, 30 patients in group 1 did not exhibit density on CT, whereas 33 patients did. 42 individuals had density on CT, compared to 21 patients who did not, according to group 2 results (21).

In 61% (44/72) of small (3 cm) nodules in cirrhosis and in 73% (44/60) of small nodules with a final diagnosis of HCC, data from perfusion US and helical CT revealed coincidental arterial hyper-vascularity, meeting the EASL noninvasive criteria. This indicates that guided biopsy is often necessary in this situation. This is especially true for nodules that are 1 to 2 cm in size, where 44% of the criteria are met, making the necessity for a biopsy measurable in over 50% of the nodules at initial observation. In 11 out of 23 of these instances, the biopsy revealed HCC (48%). Given that HCC was discovered in a small number of additional cases over a brief (three to six months) follow-up, this high prevalence may still be underestimated. Additionally, we know that the careful study of the explanted liver is the gold standard for determining diagnostic accuracy, and it may have shown foci of HCC in those nodules that were identified as high grade dysplastic nodules. This gold standard, however, does not apply to the current study, which aims to validate the European Association of Studies of Liver Noninvasive Diagnostic Criteria in Current Clinical Practice, where high grade dysplastic nodules were treated immediately and the majority of patients are not candidates for transplantation (42).

In this study we assessed the natural course of several non-neoplastic macro-nodules that were successively found by US in compensated cirrhotic individuals as part of an HCC screening program. According to our data, a subgroup at high risk of HCC is identified by macro-nodules in a cirrhotic context. Nodules on tiny biopsies that are histologically identified as high-grade dysplastic and those linked to extra nodular LCC are most likely to develop into HCC (43).

A study also showed that portal/late-phase hypo-enhancement for small HCCs and

arterial phase iso-enhancement for regenerative nodules were important imaging features that distinguished them from dysplastic nodules. The contrast enhanced ultrasonography model, which was built utilizing improved levels, did not, however, demonstrate a high degree of selective power for tiny HCC, dysplastic nodules, or regenerative nodules. The reason is that, whereas the features employed in the contrast enhanced ultrasound model were categorical variables and may not be sensitive enough to detect subtle changes during hepato-carcinogenesis, degenerative nodules would exhibit overlapping signs produced by transitional changes in the hepatic vessels during hepato-carcinogenesis. The quantitative value of CAT was examined in order to remedy this. Reduced portal perfusion in the liver parenchyma results from the arterialization of tumors during the carcinogenesis process, which also alters the normal sinusoids and portal system. As a result, CAT should vary depending on the kind of lesion. However, aside from carcinogenesis, the liver parenchyma backdrop also had an impact on the CAT result. According to a prior study, cirrhosis livers developed micro-bubbles earlier than either chronic hepatitis livers or healthy controls. The distance between the nodule and the liver hilum may also have an impact on CAT. Thus, we presented the CAT, assessing the dynamic change between the lesion and its surrounding non-lesion parenchyma, which might reduce the influence at the most of cirrhosis and distance on CAT. Since both CAT and CAT are identified by the first frame of contrast arrival, liver movement has little effect. Another benefit of CAT is its measurement reliability, in contrast to some quantitative parameters obtained from time-intensity curve analysis, such as time to peak and maximum intensity within the analysis regions of interest, which are highly dependent on the consistence of the region of interest, location, and size. In this study, the overall diagnostic performance, as measured by C, of CAT reached 0.83 for distinguishing among RN, DN, and small HCC (44).

In contrast, no invasive shunt surgery or other surgical procedures had been performed on any of the BSC patients who had regenerative nodules. These most likely had portacaval shunts, which shielded the liver's blood supply. In a related study, after an average of 80 months, only 15% of 45 children with extra-hepatic portal vein obstruction who had porto-systemic shunt surgery developed liver nodules. The vascular compensation idea in nodules that form in BCS is not supported by the current study's

opposite outcome. In fact, it's unclear if invasive treatments like TIPS contribute to the formation of these lesions. The capacity to differentiate these nodules from malignant lesions and assess the risk of developing hepatocellular carcinoma is a crucial component of the differentiation. Liver cirrhosis is linked to about 80% of HCC incidences. More than half of HCC cases are known to be caused by viral hepatitis, primarily hepatitis B and C. One study found that BCS patients had a 5-year cumulative HCC incidence rate of 7% in their large-cohort analysis. Furthermore, a recent analysis that examined 16 researchers found that the prevalence of HCC ranged widely from 2.0 to 46.2%. Countries differ in the incidence of HCC in chronic BCS, which makes for 0.7% of all HCC cases (Japan 6–41%, USA 25%, South Africa 48%). HCC rates of 6.4 and 11.3% were observed in two investigations of BCS patients with follow-up periods of 5 and 15 years, respectively. However, some of the patients in those trials also had chronic viral hepatitis or a concurrent diagnosis of BCS and HCC. This could support the idea that HCC is a result of BCS rather than its cause, or it could spark conjecture that viral hepatitis may induce HCC. Viral hepatitis did not affect any of the individuals in this investigation. 9.1% of all BCS cases had an HCC incidence rate (3/33). In patients with regenerating nodules, the occurrence rate was 13% (3/23), which was in line with the rates found in the research cited above. %). Two studies of BCS patients with follow-up periods of five and fifteen years, respectively, showed HCC rates of 6.4 and 11.3%. Nevertheless, several of the patients in those trials also had BCS and HCC diagnosed at the same time, or they also had chronic viral hepatitis. This could lead to speculation that viral hepatitis may cause HCC, or it could bolster the notion that BCS causes HCC. None of the people involved in this study had viral hepatitis. The incidence rate of HCC was 9.1% of all BCS cases (3/33). The occurrence rate in patients with regenerating nodules was 13% (3/23), consistent with the rates reported in the previously mentioned study (45).

CONCLUSION

Tri-phasic computed tomography has good diagnostic accuracy for hepatocellular carcinoma nodules as compared to cirrhosis nodules because hepatocellular carcinoma nodules show hyper- enhancement on arterial phase while cirrhosis nodules did not show hyper- enhancement on arterial phase. CT scan showed the sensitivity and specificity for HCC nodules 90% and 20% respectively. While CT scan showed the sensitivity 63% and specificity 90% for cirrhosis nodules.

Limitations:

There are some differences in the analysis and interpretation of the computed tomography images by the different radiologist which may cause misdiagnosis of the nodules. The data was only collected from 1 hospital. The sample size was limited which can affect the reliability of the results.

Recommendations:

- Future studies should have a larger sample size.
- Future studies should conduct this study in different modalities like MRI and PET.
- Radiologist should be provided with regular training sessions to interpret CT images.
- Future studies should correlate the CT images with the laboratory findings.

REFERENCES

- 1- Ward J, Robinson PJ. How to detect hepatocellular carcinoma in cirrhosis. *European radiology*. 2022 Sep;12:2258-72.
- 2- Lim JH, Kim CK, Lee WJ, Park CK, Koh KC, Paik SW, Joh JW. Detection of hepatocellular carcinomas and dysplastic nodules in cirrhotic livers: accuracy of helical CT in transplant patients. *American Journal of Roentgenology*. 2017 Sep;175(3):693-8.
- 3- Lim JH, Kim EY, Lee WJ, Lim HK, Do YS, Choo IW, Park CK. Regenerative nodules in liver cirrhosis: findings at CT during arterial portography and CT hepatic arteriography with histopathologic correlation. *Radiology*. 2020;210(2):451-8.
- 4- Baron RL, Peterson MS, Marsh W. Helical CT screening for hepatocellular carcinoma in patients with cirrhosis: frequency and causes of false-positive interpretation. *American Journal of Roentgenology*. 2013 ;180(4):1007-14.
- 5- Brancatelli G, Federle MP, Ambrosini R, Lagalla R, Carriero A, Midiri M, Vilgrain V. Cirrhosis: CT and MR imaging evaluation. *European journal of radiology*. 2007 Jan 1;61(1):57-69.
- 6- Tsochatzis EA, Bosch J, Burroughs AK. Liver cirrhosis. *The Lancet*. 2014 17;383(9930):1749-61.
- 7- Schuppan D, Afdhal NH. Liver cirrhosis. *The Lancet*. 2018 8;371(9615):838-51.
- 8- Illescas-Cárdenas J, Rodríguez-Nava P, Dena-Espinoza E. Evaluación de las lesiones hepáticas mediante tomografía multifásica multicorte: propuesta de reporte estructurado. *Anales de Radiología, Mexico*. 2017 15;16(2):87-101.
- 9- Velázquez RF, Rodríguez M, Navascués CA, Linares A, Pérez R, Sotorrios NG, Martínez I, Rodrigo L. Prospective analysis of risk factors for hepatocellular carcinoma in patients with liver cirrhosis. *Hepatology*. 2017 1;37(3):520-7.10-
- 10- SG, Boktour M, Saharia A, Li X, Ghobrial RM, Monsour Jr HP. Hepatocellular carcinoma: areview. *Journal of hepatocellular carcinoma*. 2016 5:41-53.

- 11-** Tarao K, Nozaki A, Ikeda T, Sato A, Komatsu H, Komatsu T, Taguri M, Tanaka K. Real impact of liver cirrhosis on the development of hepatocellular carcinoma in various liver diseases—meta-analytic assessment. *Cancer medicine*. 2019;8(3):1054-65.
- 12-** Sasaki K, Shindoh J, Margonis GA, Nishioka Y, Andreatos N, Sekine A, Hashimoto M, Pawlik TM. Effect of background liver cirrhosis on outcomes of hepatectomy for hepatocellular carcinoma. *JAMA surgery*. 2017 1;152(3):e165059-..
- 13-** Tsai JF, Chang WY, Jeng JE, Ho MS, Lin ZY, Tsai JH. Hepatitis B and C virus infection as risk factors for liver cirrhosis and cirrhotic hepatocellular carcinoma: A case-control study. *Liver*. 2019;14(2):98-102.
- 14-** Colombo M, de Franchis R, Del Ninno E, Sangiovanni A, De Fazio C, Tommasini M, Donato MF, Piva A, Di Carlo V, Dioguardi N. Hepatocellular carcinoma in Italian patients with cirrhosis. *New England Journal of Medicine*. 2021 5;325(10):675-80.
- 15-** Brancatelli G, Baron RL, Peterson MS, Marsh W. Helical CT screening for hepatocellular carcinoma in patients with cirrhosis: frequency and causes of false-positive interpretation. *American Journal of Roentgenology*. 2018;180(4):1007-14.
- 16-** Bolondi L. Screening for hepatocellular carcinoma in cirrhosis. *Journal of hepatology*. 2023 1;39(6):1076-84.
- 17-** Nayak A, Baidya Kayal E, Arya M, Culli J, Krishan S, Agarwal S, Mehndiratta A. Computer-aided diagnosis of cirrhosis and hepatocellular carcinoma using multi-phase abdomen CT. *International journal of computer assisted radiology and surgery*. 2019 1;14:1341-52.
- 18.** Di Martino M, Saba L, Bosco S, Rossi M, Miles KA, Di Miscio R, Lombardo CV, Tamponi E, Piga M, Catalano C. Hepatocellular carcinoma (HCC) in non-cirrhotic liver: clinical, radiological and pathological findings. *European radiology*. 2014 ;24:1446-54.
- 19.** Kudo M, Zheng RQ, Kim SR, Okabe Y, Osaki Y, Iijima H, Itani T, Kasugai H, Kanematsu M, Ito K, Usuki N. Diagnostic accuracy of imaging for liver cirrhosis compared to histologically proven liver cirrhosis. *Intervirology*. 2018;51(Suppl. 1):17-26.

- 20.** Singal AG, Zhang E, Narasimman M, Rich NE, Waljee AK, Hoshida Y, Yang JD, Reig M, Cabibbo G, Nahon P, Parikh ND. HCC surveillance improves early detection, curative treatment receipt, and survival in patients with cirrhosis: a meta-analysis. *Journal of hepatology*. 2022 1;77(1):128-39.
- 21.** Davila JA, Morgan RO, Richardson PA, Du XL, McGlynn KA, El-Serag HB. Use of surveillance for hepatocellular carcinoma among patients with cirrhosis in the United States. *Hepatology*. 2020;52(1):132-41.
- 22.** Ayuso C, Rimola J, García-Criado Á. Imaging of HCC. *Abdominal imaging*. 2017 ;37:215-30.
- 23.** Hyodo T, Murakami T, Imai Y, Okada M, Hori M, Kagawa Y, Kogita S, Kumano S, Kudo M, Mochizuki T. Hypovascular nodules in patients with chronic liver disease: risk factors for development of hypervascular hepatocellular carcinoma. *Radiology*. 2013;266(2):480-90.
- 24.** Forner A, Vilana R, Ayuso C, Bianchi L, Solé M, Ayuso JR, Boix L, Sala M, Varela M, Llovet JM, Brú C. Diagnosis of hepatic nodules 20 mm or smaller in cirrhosis: prospective validation of the noninvasive diagnostic criteria for hepatocellular carcinoma. *Hepatology*. 2015;47(1):97-104.
- 25.** Bolondi L, Gaiani S, Celli N, Golfieri R, Grigioni WF, Leoni S, Venturi AM, Piscaglia F. Characterization of small nodules in cirrhosis by assessment of vascularity: the problem of hypovascular hepatocellular carcinoma. *Hepatology*. 2015 ;42(1):27-34.
- 26.** Sangiovanni A, Alimenti E, Gattai R, Filomia R, Parente E, Valenti L, Marzi L, Pellegatta G, Borgia G, Gambato M, Terreni N. Undefined/non-malignant hepatic nodules are associated with early occurrence of HCC in DAA-treated patients with HCV-related cirrhosis. *Journal of hepatology*. 2020 1;73(3):593-602.
- 27.** Matsui O, Kadota M, Kameyama T, Yoshikawa J, Takashima T, Nakanuma Y, Unoura M, Kobayashi K, Izumi R, Ida M. Benign and malignant nodules in cirrhotic livers: distinction based on blood supply. *Radiology*. 2021;178(2):493-7.
- 28.** Krinsky GA, Lee VS, Theise ND, Weinreb JC, Rofsky NM, Diflo T, Teperman LW. Hepatocellular carcinoma and dysplastic nodules in patients with cirrhosis: prospective diagnosis with MR imaging and explantation correlation. *Radiology*. 2001;219(2):445-54.

29. Borzio M, Fargion S, Borzio F, Fracanzani AL, Croce AM, Stroffolini T, Oldani S, Cotichini R, Roncalli M. Impact of large regenerative, low grade and high grade dysplastic nodules in hepatocellular carcinoma development. *Journal of hepatology*. 2003 1;39(2):208-14.
30. Kondo F, Ebara M, Sugiura N, Wada K, Kita K, Hirooka N, Nagato Y, Kondo Y, Ohto M, Okuda K. Histological features and clinical course of large regenerative nodules: evaluation of their precancerous potentiality. *Hepatology*. 2003;12(3):592-8.
31. Lin WR, Lim SN, McDonald SA, Graham T, Wright VL, Peplow CL, Humphries A, Kocher HM, Wright NA, Dhillon AP, Alison MR. The histogenesis of regenerative nodules in human liver cirrhosis. *Hepatology*. 2010;51(3):1017-26.
32. Sato T, Kondo F, Ebara M, Sugiura N, Okabe S, Sunaga M, Yoshikawa M, Suzuki E, Ogasawara S, Shinozaki Y, Ooka Y. Natural history of large regenerative nodules and dysplastic nodules in liver cirrhosis: 28-year follow-up study. *Hepatology International*. 2015;9:330-6.
33. Brancatelli G, Federle MP, Grazioli L, Golfieri R, Lencioni R. Benign regenerative nodules in Budd-Chiari syndrome and other vascular disorders of the liver: radiologic-pathologic and clinical correlation. *Radiographics*. 2012;22(4):847-62.
34. Lim JH, Kim EY, Lee WJ, Lim HK, Do YS, Choo IW, Park CK. Regenerative nodules in liver cirrhosis: findings at CT during arterial portography and CT hepatic arteriography with histopathologic correlation. *Radiology*. 2020 Feb;210(2):451-8.
35. Duan Y, Xie X, Li Q, Mercaldo N, Samir AE, Kuang M, Lin M. Differentiation of regenerative nodule, dysplastic nodule, and small hepatocellular carcinoma in cirrhotic patients: A contrast-enhanced ultrasound–based multivariable model analysis. *European Radiology*. 2020;30:4741-51.
36. Tüysüz U, Batı İB. Characteristics of Regenerative Nodules and Their Relationship with Hepatocellular Carcinoma in Budd-Chiari Syndrome, and Role of Computed Tomography in Diagnosis and Follow-Up. *Indian Journal of Surgery*. 2024;86(1):172-8.
37. Kim JA, Ahn HS, Park H, Seo YR, Seo JH, Kim CW, Kim HY. Hepatocellular carcinoma hidden by multiple infarcted regenerative nodules. *The Korean Journal of Internal Medicine*. 2016;31(6):1178.
38. Thaïss WM, Kaufmann S, Kloth C, Nikolaou K, Bösmüller H, Horger M. VEGFR-2

expression in HCC, dysplastic and regenerative liver nodules, and correlation with pre-biopsy Dynamic Contrast Enhanced CT. *European Journal of Radiology*. 2016 1;85(11):2036-41.

39. Nagasue N, Yukaya H, Chang YC, Kimura N, Ota N, Nakamura T. Hepatocellular pseudotumour (regenerating nodule) in the cirrhotic liver mimicking hepatocellular carcinoma. *British journal of surgery*.2013;75(11):1124-8.

40. Choi BI, Takayasu K, Han MC. Small hepatocellular carcinomas and associated nodular lesions of the liver: pathology, pathogenesis, and imaging findings. *AJR. American journal of roentgenology*. 2003;160(6):1177-87.

41. Kanematsu M, Hoshi H, Yamada T, Murakami T, Kim T, Kato M, Yokoyama R, Nakamura H. Small hepatic nodules in cirrhosis: ultrasonographic, CT, and MR imaging findings. *Abdominal imaging*. 2017;24:47-55.

42. Elsayes KM, Hooker JC, Agrons MM, Kielar AZ, Tang A, Fowler KJ, Chernyak V, Bashir MR, Kono Y, Do RK, Mitchell DG. 2017 version of LI-RADS for CT and MR imaging: an update. *Radiographics*. 2017;37(7):1994-2017.

43. Bolondi L, Gaiani S, Celli N, Golfieri R, Grigioni WF, Leoni S, Venturi AM, Piscaglia F. Characterization of small nodules in cirrhosis by assessment of vascularity: the problem of hypovascular hepatocellular carcinoma. *Hepatology*. 2005 ;42(1):27-34.

44. Borzio M, Fargion S, Borzio F, Fracanzani AL, Croce AM, Stroffolini T, Oldani S, Cotichini R, Roncalli M. Impact of large regenerative, low grade and high grade dysplastic nodules in hepatocellular carcinoma development. *Journal of hepatology*. 2013 1;39(2):208-14..

45. Duan Y, Xie X, Li Q, Mercaldo N, Samir AE, Kuang M, Lin M. Differentiation of regenerative nodule, dysplastic nodule, and small hepatocellular carcinoma in cirrhotic patients: A contrast-enhanced ultrasound based multivariable model analysis. *European Radiology*. 2020 ;30:4741-51.

46. Tüysüz U, Batı İB. Characteristics of Regenerative Nodules and Their Relationship with Hepatocellular Carcinoma in Budd-Chiari Syndrome, and Role of Computed Tomography in Diagnosis and Follow-Up. *Indian Journal of Surgery*. 2024;86(1):172-8.

47. Sersté T, Barrau V, Ozenne V, Vullierme MP, Bedossa P, Farges O, Valla DC, Vilgrain V, Paradis V, Degos F. Accuracy and disagreement of computed tomography

and magnetic resonance imaging for the diagnosis of small hepatocellular carcinoma and dysplastic nodules: role of biopsy. *Hepatology*. 2012 ;55(3):800-6.

48. Takayasu K, Moriyama N, Muramatsu Y, Makuuchi M, Hasegawa H, Okazaki N, Hirohashi S. The diagnosis of small hepatocellular carcinomas: efficacy of various imaging procedures in 100 patients. *AJR. American journal of roentgenology*. 2020;155(1):49-54.

49. Forner A, Vilana R, Ayuso C, Bianchi L, Solé M, Ayuso JR, Boix L, Sala M, Varela M, Llovet JM, Brú C. Diagnosis of hepatic nodules 20 mm or smaller in cirrhosis: prospective validation of the noninvasive diagnostic criteria for hepatocellular carcinoma. *Hepatology*. 2008;47(1):97-104.

50. Lee YJ, Lee JM, Lee JS, Lee HY, Park BH, Kim YH, Han JK, Choi BI. Hepatocellular carcinoma: diagnostic performance of multidetector CT and MR imaging—a systematic review and meta-analysis. *Radiology*. 2015 ;275(1):97-109.

51. Kudo M, Zheng RQ, Kim SR, Okabe Y, Osaki Y, Iijima H, Itani T, Kasugai H, Kanematsu M, Ito K, Usuki N. Diagnostic accuracy of imaging for liver cirrhosis compared to histologically liver cirrhosis. *Intervirolgy*.2013;51(Suppl. 1):17-26.

52. Nam CY, Chaudhari V, Raman SS, Lassman C, Tong MJ, Busuttil RW, Lu DS. CT and MRI improve detection of hepatocellular carcinoma, compared with ultrasound alone, in patients with cirrhosis. *Clinical Gastroenterology and Hepatology*. 2011 1;9(2):161-7.

53. Nadarevic T, Giljaca V, Colli A, Fraquelli M, Casazza G, Miletic D, Štimac D. Computed tomography for the diagnosis of hepatocellular carcinoma in adults with chronic liver disease. *Cochrane database of systematic reviews*. 2021(10):127-9.

54. Takayasu K, Furukawa H, Wakao F, Muramatsu Y, Abe H, Terauchi T, Winter 3rd TC, Sakamoto M, Hirohashi S. CT diagnosis of early hepatocellular carcinoma: sensitivity, findings, and CT-pathologic correlation. *AJR. American journal of roentgenology*. 2005;164(4):885-90.

ENGLISH CONSENT FORM

The study you are about to participate is a randomized control trial survey titled as;

**“Assessment of Diagnostic Accuracy of Tri-phasic Computed
Tomography in Differentiating Cirrhosis Nodules from
Hepatocellular Carcinoma Nodules”**

The study has no potential harm to participants. All data collected from you will be coded in order to protect your identity, and should not be disclosed to anyone. Following the study there will be no way to connect your name with your data. Your answers to the questions will not affect the quality of education given to you. Any additional information about the study results will be provided to you at its conclusion, upon your request.

You are free to withdraw from the study at any time. You agree to participate, indicating that you have read and understood the nature of the study, and that all your inquiries concerning the activities have been answered to your satisfaction.

NAME _____

SIGNATURE _____

DATE _____

URDU CONSENT FORM

میں _____ تصدیق کرتا/ کرتی ہوں کہ محترمہ (ارامہ) نے اپنی اس تحقیق

“Assessment of Diagnostic Accuracy of Tri-phasic Computed Tomography in Differentiating Cirrhosis Nodules from Hepatocellular Carcinoma Nodules”

زیرنگرانی (ہر باطلو تب) کے متعلق بتا دیا ہے۔ مجھے اس تحقیق کی نوعیت، مقاصد، احداث، توقعات، فوائد اور خطرات کے متعلق، ساری معلومات فراہم کر دی گئی ہیں اس تحقیق کے دوران ساری معلومات صیغہ راز میں رہیں گی اور مریض کا نام اور دیگر معلومات صرف تحقیق کے لیے استعمال ہوں گی۔ مجھے یہ بھی بتا دیا گیا ہے کہ میں اس تحقیق سے متعلق ہر قسم کے سوال پوچھنے کا مجاز ہوں اور یہ تحقیق صرف ایک شخص کا مفاد میں نہیں ہے بلکہ بحسبیت مجموعی انسانیت کا مفاد اس سے وابستہ ہے۔ تمام تفصیلات جاننے کے بعد یس تحقیق میں شامل ہونے یا نہ ہونے پر کسی کا قائل نہیں ہوں۔ اس تحقیق سے کسی بھی وقت علیحدہ ہونے پر مجھ پر کوئی پابندی نہیں ہو گی۔ میں بذاتِ خود بقائمی حوش و حواس اور رضا مندی سے اس تحقیقاتی عمل میں شامل ہوتی/ ہوتا ہوں۔

دستخط محقق _____

دستخط شرکت کار _____

تاریخ _____

QUESTIONNAIRE

Name: _____

Age: _____

Contact No. _____

1-How many numbers of nodules present in liver?

- a) None
- b) 1
- c) 2-4
- d) >4

2- If nodules present than how many No. of cirrhotic nodules present in liver?

- a) 1cm
- b) 2-4cm
- c) >4cm

3- What is the size of cirrhotic nodules present in liver?

- a) <2cm
- b) 2cm
- c) 3-5cm
- d) >5cm

4- What is the Density on CT?

- a) Iso-dense
- b) Hypo-dense
- c) Hyper-dense

5- What is the enhancement of nodules on CT?

- a) Arterial phase
- b) Portal venous phase
- c) Delayed phase

6- How many no. of nodules present in liver?

- a) 1cm
- b) 2-4 cm
- c) >4cm

7- What is the size of hepatocellular carcinoma nodules in liver?

- a) <2cm
- b) 2cm
- c) 3-5cm
- d) >5cm

8- What is the density on CT?

- a) Iso-dense
- b) Hypo-dense
- c) Hyper-dense

9- What is the enhancement of nodules on CT?

- a) Arterial phase
- b) Portal venous Phase
- c) Delayed phase



OFFICE OF THE DEAN-FAHS

Ref.: IRB /FAHS/Allied-

HS/10/24/MS/RS-3511

Date: 29th October 2024

Name: Ammara Jabeen (MS Allied Health Sciences)

Registration: SU91-MSAHW-S23-017

Subject: Ethical Approval Letter

The Research Ethical Committee convened on Dated: **17th October, 2024** to discuss your protocol titled “**Assessment of diagnostic accuracy of triphasic CT in differentiating cirrhosis nodules from hepatocellular carcinoma nodules.**”

No further corrections and recommendations were suggested. The above-mentioned protocol has been approved after considering various research issues including ethical concerns with condition that the researcher will submit completion report at the end of his/her research.

Prof. Dr. Muhammad Naveed
Babur Dean/Convener REC
Faculty of Allied Health
Sciences Superior University,
Lahore

