

## EVALUATING THE RELATIONSHIP BETWEEN HEPATIC ARTERY BUFFER RESPONSE AND HEPATITIS B/C IN CHRONIC LIVER DISEASE PATIENTS

Hafiz Habib Ur Rehman<sup>\*1</sup>, Muhammad Adnan Hafeez<sup>2</sup>

<sup>\*1</sup>Department of Radiological Sciences and Medical Imaging Technology, Faculty of Allied Health Sciences, Superior University Lahore

<sup>2</sup>Department of Human Nutrition and Food Technology, Faculty of Allied Health Sciences, Superior University Lahore

<sup>1</sup>habiburrehman7915@gmail.com, <sup>2</sup>adnan.hafeez@superior.edu.pk

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Corresponding Author: \*

Hafiz Habib Ur

Rehman

### Abstract

Hepatic artery buffer response (HABR) is the compensatory increase in hepatic arterial flow that occurs when portal venous flow decreases, helping maintain liver perfusion in chronic liver disease. The aim of this study was to compare portal-vein and hepatic-artery Doppler parameters between patients with HBV- and HCV-related chronic liver disease and to evaluate these parameters as indirect markers of portal–arterial haemodynamic adaptation related to HABR. A cross-sectional analytical study included 60 chronic liver disease patients at Farooq Hospital, Lahore. Participants were selected through non-probability sampling and examined using abdominal Doppler ultrasonography. Portal vein diameter, portal vein mean flow velocity, hepatic artery peak systolic velocity (PSV), end-diastolic velocity (EDV), resistive index (RI), and pulsatility index (PI) were recorded. Data were analysed using descriptive statistics, independent-samples t-tests, and Pearson correlation. HCV patients had lower portal vein flow velocity than HBV patients (14.94 vs 16.80 cm/s) but higher hepatic artery PSV (49.01 vs 44.52 cm/s), RI (0.72 vs 0.66), and PI (1.37 vs 1.23). Significant differences were found for portal vein velocity ( $p = 0.026$ ), PSV ( $p = 0.044$ ), RI ( $p = 0.005$ ), and PI ( $p = 0.014$ ), whereas EDV was non-significant ( $p = 0.367$ ). Portal vein velocity was negatively correlated with PSV ( $r = -0.463$ ), RI ( $r = -0.512$ ), and PI ( $r = -0.421$ ). HCV patients demonstrated greater portal–arterial hemodynamic alteration than HBV patients. Doppler ultrasonography may support the non-invasive assessment of HABR in chronic viral liver disease.

## INTRODUCTION

### Chapter 1

The liver is the largest solid visceral organ of the human body and is defined as a highly specialized metabolic, synthetic, detoxifying, and immunological organ located in the right upper quadrant of the abdomen. It is composed mainly

of hepatocytes, which are arranged in functional units known as hepatic lobules. Through these cellular and vascular structures, the liver performs essential functions required for survival and internal homeostasis (1). In an adult, the liver weighs approximately 1.4–1.6 kg and represents nearly 2% of total body weight. Its strategic

anatomical position between the gastrointestinal tract and systemic circulation allows it to process absorbed nutrients, regulate biochemical substances, and remove potentially harmful compounds before they enter the general circulation (2).

The hepatic vascular anatomy describes the well-defined pattern of blood vessels that bring blood to the liver, move blood within the liver, and carry blood away from the liver into the systemic venous circulation. Liver has a unique blood supply with two primary blood vessels, portal vein and hepatic artery. The portal vein provides about 70-75% of all hepatic blood flow, and the hepatic artery provides almost 25-30% (3). Although both blood vessels contribute an unequal amount of volume, both are physiologically significant: the portal vein carries the majority of blood rich in nutrients from the gastrointestinal tract and the hepatic artery carries oxygenated arterial blood. In adults, the total hepatic blood flow is normally about 1.2-1.5 L/min, accounting for a significant percentage of the resting cardiac output. This high perfusion is required because it is a continuous process that the liver performs in which absorbed nutrients are continuously processed, venous blood from the splanchnic organs is filtered and biochemical stability is maintained in the body (4).

The portal vein is a low pressure, high capacitance vessel that is primarily formed by the confluence of the superior mesenteric and splenic veins, plus venous drainage of the stomach, pancreas, gall bladder and intestines. Carries partially oxygenated but nutrient rich blood after absorption in the intestine to the liver. Portal venous pressure is normally low (5-10 mmHg), and portal flow is normally hepatopetal; however, flow may become bidirectional or hepatofugal in advanced portal hypertension (5). The portal vein enters the porta hepatis and then splits into right and left branches, which then split again into segmental and interlobular portal venules. The small venous branches are contained in the portal triads along with branches of the bile duct and hepatic artery. Because the portal venous system places substances from the gut directly into the hepatocyte for metabolism, storage, detoxification

and conversion prior to entering the systemic circulation, the portal venous system is therefore central to hepatic physiology (6).

The hepatic artery is a low volume, high pressure vascular supply which typically originates from the common hepatic artery (branch of the celiac trunk). Passes through the porta hepatis and forms right and left hepatic arterial branches in a similar distribution with the portal venous branches (7). It supplies a relatively small proportion of the total hepatic blood flow but the blood in the hepatic artery has a higher oxygen concentration and thus supplies a large proportion of the oxygen to the hepatic tissue. Under all physiological conditions the oxygen consumption of hepatocytes is high, and portal venous blood does not provide sufficient oxygen. The terminal arterioles are the end result of the hepatic arterial branches which drain into the hepatic sinusoids. This way, the blood of the arteries and the portal veins is mixed before reaching the hepatocytes and at the same time oxygen, nutrients, hormones and other substances circulating in the blood are delivered to the hepatocytes (8).

Hepatic artery buffer response is an inherent autoregulatory mechanism that is manifested by inversely related changes in hepatic arterial blood flow to changes in portal venous blood flow. Hepatic arterial flow increases in response to a decrease in portal venous inflow by vasodilation of hepatic arterial resistance vessels. Hepatic arterial flow tends to diminish with the rise in portal venous inflow due to relative vasoconstriction (9). This response tends to reduce or normalize total hepatic blood flow but cannot fully compensate for the portal venous flow that is lost. This is particularly relevant because portal venous flow is largely passive and dependent on splanchnic venous return, while hepatic arterial flow is regulated by vascular tone. Thus, the hepatic artery is the variable blood supply to the liver and the portal vein is the major but less active variable blood supply (10).

The hepatic artery buffer response most commonly is believed to be related to the washout of adenosine. Adenosine is constantly formed around terminal hepatic arterial resistance vessels

and in the periportal region. When liver blood flow through the portal vein is normal, adenosine is washed out to moderate the hepatic arterial vasodilation. The washout of adenosine is decreased when portal venous flow is decreased. This causes adenosine to accumulate at the Hepatic Arterial Resistance Vessel and stimulates the adenosine receptors causing vasodilation. Hepatic arterial blood flow increases when the resistance to blood flow in the arteries of the liver decreases. Conversely, with an increase in portal venous flow, there is a faster washout of adenosine, a lower concentration of adenosine in the local area, and a greater tone of the hepatic arteries. This reciprocity is a sensitive local mechanism by which the liver can regulate arterial inflow in relation to changes in portal venous inflow (11).

The increase in intrahepatic vascular resistance is the main hemodynamic consequence of chronic liver disease. The blood in the portal vein circulates through the liver at low pressure, but fibrosis, nodule formation, narrowing of sinusoids and changes in the blood vessels impede the flow of blood. With rising resistance, portal venous pressure also rises and portal blood flow may become slower, turbulent or redistributed (12). This is called portal hypertension. portal hypertension is not only structural in nature but also dynamic. Vascular tone is increased by the release of vasoconstrictor substances (endothelin) and the decrease in nitric oxide availability is seen within the liver. The activated stellate cells and vascular smooth muscle cells additionally contract the sinusoidal and perisinusoidal spaces. Thus, chronic liver disease leads to anatomical and functional narrowing of the hepatic microcirculation (13).

Hepatitis B and C are significant viral causes of chronic liver disease, accounting for a large fraction of the progressive liver injury in the world. Chronic viral hepatitis is the prolonged presence of hepatotropic viruses in the liver for more than 6 months that results in ongoing liver inflammation, immune-mediated injury and fibrosis (14). The Hepadnaviridae family of viruses includes partially double-stranded DNA virus such

as hepatitis B virus, while the Flaviviridae family is a group of single-stranded RNA viruses, including hepatitis C virus. While both viruses damage the liver primarily through the hepatocyte, and can cause chronic liver damage, they have different virological structures, patterns of replication, interactions with the immune system and disease progression. These differences are significant as they will affect the course and the rate of liver damage in infected individuals (15).

Hepatitis B virus infection becomes chronic if the immune system does not destroy the virus after the first exposure. Typically, chronic Hepatitis B is diagnosed if the Hepatitis B surface antigen is positive for over 6 months. HBV is unusual in the following regard: after infection, covalently closed circular DNA is formed in the nucleus of the infected hepatocyte. This viral reservoir may be responsible for persistence of infection even if viral replication is decreased. HBV-induced liver damage is predominantly immune-mediated and not cytopathic. Infected hepatocytes are recognized by CTLs, which trigger inflammatory destruction of liver cells. Over time, hepatocyte damage and regeneration induce and activate fibrogenic pathways, resulting in the accumulation of extracellular matrix, bridging fibrosis, and cirrhosis in some patients (16).

Hepatitis C virus (HCV) infection is also associated with chronic liver disease as a frequent complication (when the virus does not clear spontaneously after acute infection). If anti-HCV antibody is present, plus evidence of chronic infection, usually in the form of HCV RNA testing, then chronic Hepatitis C is diagnosed. Chronic viral hepatitis can vary based on the interplay of viral, immune, host, duration of infection, age, metabolic status and other comorbidities. Hepatic stellate cells are the key cells in the pathogenesis of fibrosis, which are activated by persistent necroinflammation in both HBV and HCV infection (17). However, when activated, stellate cells synthesize collagen and other components of the extracellular matrix in the space of Disse and portal areas. This process slowly turns the normal liver tissue into fibrotic tissue. Over time fibrous septa grow between

portal tracts and central veins and regenerative nodules grow. This is because these changes impair normal sinusoidal exchange and disrupt the organized vascular architecture of the liver and result in chronic viral hepatitis progressing to advanced chronic liver disease or cirrhosis (18).

Hepatitis B and Hepatitis C both can lead to chronic liver disease but the damage that they cause is not the same. While HBV can enter immune tolerant, immune active, inactive carrier and reactivation stages, HCV tends to cause a gradual progression to fibrosis and chronic low-grade inflammation (19). HBVs are also highly linked to HCC due to the chronic inflammation and genomic effect of the virus; HCV-induced carcinogenesis is generally closely related to advanced fibrosis and cirrhosis. These differences suggest that the viral etiology of chronic liver disease may affect the course of the disease. Thus, it is important to recognize the difference between Hepatitis B and Hepatitis C as two forms of chronic liver disease that contribute to the development of chronic liver inflammation, fibrosis and cirrhosis in order to assess vascular and hemodynamic changes in chronic liver disease patients.

Hepatic hemodynamic alteration is the term used for the alteration of blood flow, vascular resistance, pressure gradient and perfusion pattern in the liver. These changes are slow to develop in chronic liver disease associated with Hepatitis B or Hepatitis C infection, and are a consequence of the associated inflammation, fibrosis and architectural distortion, which disrupt normal portal venous inflow, hepatic arterial inflow, sinusoidal circulation, and hepatic venous drainage (21). A significant amount of portal venous blood flows through the sinusoids in the liver with minimal increase in pressure. In chronic viral liver disease, however, intrahepatic resistance is progressively raised by fibrotic septa, regenerative nodules, sinusoidal capillarisation, endothelial abnormalities and vascular remodelling. This resistance causes a normal portal vein to hepatic artery pressure flow relationship that does not occur normally (22).

In chronic liver disease the portal venous system is

typically the first and most prominently involved part of the liver circulation. During the evolution of fibrosis, the resistance to portal venous inflow rises presinusoidal, sinusoidal and postsinusoidal. This can cause an increase in portal venous pressure and a progressive increase in portal hypertension (12). Normally portal venous blood flows towards the liver, but during advanced disease portal venous blood flow can be reduced, slow, bidirectional or even hepatofugal. The portal vein velocity can be reduced due to decreased capacity to receive and conduct portal blood within the liver's microcirculation. Collateral circulation, splenic congestion, splenomegaly, ascites and gastroesophageal varices can also result from increased portal pressure. Thus, decreased portal flow is not only a vascular phenomenon, but it also reflects increasing hepatic structural damage (23).

In chronic viral liver disease, hepatic arterial circulation also is altered, along with portal venous changes. Compensatory changes of the hepatic artery may occur to maintain oxygenation of the liver as portal venous perfusion decreases. This can be seen as a rise in hepatic arterial flow velocity, changes in peak systolic velocity, changes in end diastolic velocity and variations in hepatic artery resistive index (24). The hepatic artery RI is a reflection of downstream vascular resistance and it is derived from the systolic and diastolic flow velocities. An elevated resistive index could indicate elevated intrahepatic vascular resistance, decreased arterial compliance or poor microvascular perfusion. In chronic liver disease, the hepatic artery becomes more important due to less contribution from the portal vein. However, the effectiveness of this arterial compensation may decrease as cirrhosis and endothelial dysfunction become more advanced (25).

HBV- and HCV-related chronic liver disease can have some similarities in their hemodynamic profile, but the vascular effect may not be completely alike. Hepatitis B can go through intermittent stages of viral activity, immune mediated hepatocyte damage, necroinflammation, fibrosis and cirrhosis. Structural and vascular changes can be accelerated in some patients, due

to rapid inflammatory activity or repeated viral reactivation. Hepatitis C, in contrast, may cause chronic, low-grade inflammation, oxidative stress and metabolic abnormality of steatosis, and progressive fibrosis over many years. These various biological pathways can affect the extent of sinusoidal injury, endothelial dysfunction, portal resistance and arterial compensation. Hence, patients with chronic liver disease due to HBV and HCV might present with differences in portal vein velocity, hepatic artery resistance, and the overall portal-arterial flow redistribution (26).

The RI of the hepatic artery is one of the most commonly used Doppler indices for the evaluation of hepatic vessels. This is determined by peak systolic velocity – end diastolic velocity divided by peak systolic velocity. Higher RI suggests increased downstream resistance and relatively decreased diastolic flow, lower RI may suggest decreased arterial resistance or vasodilatation (27). The pulsatility index, which is based on the velocity components of the systolic, diastolic and mean component of the arterial waveform, is another index used to describe the variability of arterial waveforms. These arterial parameters are not used in isolation when evaluating HABR, but in conjunction with portal venous flow. A higher arterial flow or change in arterial resistance may be a compensatory (indirect Doppler) sign of hepatic artery buffer response (28) when portal venous flow is decreased.

Therefore, the assessment of HABR in Doppler ultrasound is done based on the relationship between the PV and HA parameters. The Doppler study should include both the hepatic artery and the portal vein, because HABR is a physiological change and the flow of the hepatic artery changes in relation to the portal venous flow. When portal vein velocity is reduced and hepatic artery peak systolic velocity, end diastolic velocity, resistive index or pulsatility index is altered, this may indicate compensatory portal-arterial redistribution (29). Patients are typically tested after a fast, while lying on their back, in a quiet breathing state and with standardized Doppler parameters (gain, wall filter, sample volume, and angle correction). Doppler ultrasound is a useful

clinical approach to evaluate hepatic hemodynamic adaptation in patients with chronic liver disease by simultaneously measuring portal and hepatic arterial parameters. It is also important to comprehend if the hepatic hemodynamic pattern is similar or different among chronic liver disease from Hepatitis B and Hepatitis C. Both viruses can lead to fibrosis and cirrhosis, but the immunology, inflammatory pattern, and virology and progression may be different (30). These differences may have a modulating effect on portal venous velocity, peak systolic velocity of the hepatic artery, end diastolic velocity of the hepatic artery, resistive index, pulsatility index and overall portal-arterial flow redistribution. Comparisons of these parameters may be useful for determining if there is an association between hepatic arterial compensation and viral etiology. This is particularly relevant in clinical practice where Doppler ultrasound becomes a non-invasive, repeatable, radiation-free and inexpensive technique to assess hepatic blood flow (31).

Thus, the present study is needed to better understand Doppler based hepatic artery buffer response in patients with chronic liver disease- Hepatitis B and Hepatitis C. It could serve as a helpful reference for non-invasive hemodynamic assessment and might aid the interpretation of portal and hepatic arterial Doppler parameters in chronic viral liver disease. This study aims to assess the correlation between Hepatitis B/C and Hepatic Artery Buffer Response, by Doppler ultrasound, in chronic liver disease patients.

#### **AIM AND OBJECTIVES**

The aim of this study was to evaluating the relationship between hepatic artery buffer response and hepatitis b/c in chronic liver disease patients. The objective of this study were:

- To evaluate the relationship between hepatic artery buffer response and Hepatitis B and Hepatitis C in patients with chronic liver disease using Doppler ultrasound.
- To measure portal vein Doppler parameters in chronic liver disease patients with Hepatitis B and Hepatitis C.

- To assess hepatic artery Doppler parameters, including resistive index, in patients with chronic viral hepatitis.

## Chapter 2

### LITERATURE REVIEW

Sajid et al. (2025) used a cross-sectional diagnostic accuracy methodology in Quetta, Pakistan, to determine the role of portal vein Doppler ultrasonography in the non-invasive assessment of chronic liver disease. The study was conducted at the Department of Diagnostic Radiology, Bolan Medical College and Hospital, from January to July 2025. A total of 200 patients aged 18–70 years with clinically suspected chronic liver disease underwent standardized portal vein Doppler ultrasound followed by ultrasound-guided liver biopsy. The main aim was to compare Doppler findings with histopathological confirmation using METAVIR staging as the gold standard. The study assessed portal vein diameter, flow velocity, flow direction, collateral vessels, hepatic venous waveform, and hepatic artery resistive index. The authors found that Doppler ultrasound showed 94.4% sensitivity, 78.5% specificity, and 90% overall diagnostic accuracy. Reduced portal vein velocity below 16 cm/s combined with hepatic artery RI above 0.80 strongly predicted chronic liver disease (32).

In a descriptive cross sectional validation study, Fida et al. (2025) evaluated the diagnostic utility of Doppler hepatic vein waveform patterns in the diagnosis of cirrhosis in chronic hepatitis C patients in Mardan, Pakistan. This study was carried out in the Department of Radiology Mardan Medical College from January to September 2025. Patients with chronic HCV infection were selected using non-probability consecutive sampling to include 96 patients age 18-60 years. The objectives were to assess the performance of colour Doppler ultrasound in detecting cirrhotic changes by detecting abnormal hepatic venous waveforms with histopathology as the reference standard. The hepatic venous waveforms were triphasic, biphasic, or monophasic. Doppler ultrasound was determined to be 90.7% sensitive, 76.2% specific, 83.0%

positive predictive value, 86.5% negative predictive value and 84.3% diagnostic accuracy in this study. The results validate ultrasound Doppler as a valuable non-invasive technique for the diagnosis of HCV-related cirrhosis (33).

Latheef et al. (2025) used a prospective observational methodology in Vijayapura, India, to evaluate the correlation between hepatic vein waveform changes on Doppler ultrasound and severity of cirrhosis. The study was done at Shri BM Patil Medical College Hospital and Research Centre and consisted of 140 patients clinically and radiologically diagnosed as cirrhosis. The purpose was to see if hepatic vein waveforms were related to the severity of cirrhosis (Child-Pugh classification). The hepatic venous waveforms were classified as triphasic, biphasic and monophasic using Doppler echo, and these results were correlated with Child-Pugh classes A, B and C. The authors determined that the severity of the disease correlated significantly with wave form abnormality. The monophasic and biphasic waveforms were more common in Child-Pugh class C and the triphasic waveforms were more common in Child-Pugh class A. Based on the results of the study, hepatic vein waveform analysis is a useful, non-invasive tool for the assessment of the severity of cirrhosis (34).

Using a cohort study design in Turkey, Çolakoğlu Er et al. (2025) investigated the changes in portal venous flow velocity in chronic hepatitis C patients before and after direct-acting antiviral therapy. A total of 53 CHC patients and 55 healthy age and sex matched controls were enrolled in the study. The purpose was to assess whether successful antiviral therapy will enhance portal venous hemodynamics and/or non-invasive fibrosis markers. Before and after treatment, portal vein flow velocity was measured using Doppler ultrasonography, and biochemical markers, APRI and FIB-4 score were also evaluated. Pretreatment portal vein velocity was significantly lower in the chronic hepatitis C patients than in the control patients, the study found. All patients had sustained virological response after direct-acting antiviral therapy, and portal vein velocity was significantly increased

from  $12.12 \pm 2.81$  cm/s to  $17.61 \pm 4.65$  cm/s. The results indicate that the possible improvement in portal circulation and hemodynamic disturbance with HCV eradication (35).

In a cross-sectional study, Hassan et al. (2025) compared liver stiffness measurement (LSM), Doppler ultrasonography (DU), and non-invasive serum markers as predictors of varices and variceal bleeding in cirrhotic patients in Egypt. A total of 144 cirrhotic patients were included and divided into three groups: No varices, Non-bleeding varices and Variceal bleeding. The goal was to compare the performance of non-invasive procedures such as Doppler ultrasound for varice diagnosis and risk of bleeding. The Doppler parameters assessed were portal vein hemodynamic parameters while liver stiffness measurement, FIB-4, APRI, and platelet count/spleen diameter ratio were other tools used. The study revealed that the liver stiffness measurement and certain blood markers performed better in the diagnosis of variceal bleeding than Doppler ultrasound. Doppler parameters were still useful to describe portal hemodynamic changes in cirrhosis, however. The Doppler results of this study should be viewed as hemodynamically driven parameters and not as solely predictive of complications (36).

The authors of Tuladhar et al. (2024) employed an observational Doppler ultrasonography approach in Nepal to evaluate hepatic arterial hemodynamics in CLD patients. A total of 50 patients were included in the study and the objective was to investigate the correlation between the hepatic artery Doppler parameters and the Model for End-Stage Liver Disease (MELD) score. Liver size, portal vein size, portal vein flow, hepatic artery peak systolic velocity, end diastolic velocity, hepatic artery resistive index, hepatic artery pulsatility index and acceleration time were assessed sonographically. MELD score was calculated using biochemical parameters such as bilirubin, creatinine and international normalized ratio. The study found mean hepatic artery PSV of  $107.42 \pm 48.10$  cm/s, EDV of  $26.40 \pm 14.68$  cm/s, RI of  $0.74 \pm 0.06$ , and PI of  $1.47 \pm 0.24$ . Although hepatic artery parameters did not

show significant correlation with MELD score, high RI values were common in chronic liver disease patients (37).

In their study from Egypt, Ellaban et al. (2024) have chosen prospective study methodology to compare Doppler ultrasound and shear wave elastography methods for liver cirrhosis diagnosis. The study involved 100 patients with advanced liver fibrosis/cirrhosis and sought to see if Doppler ultrasound could detect morphological and hemodynamic vascular changes related to cirrhosis. Patients had shear wave elastography and Doppler ultrasound evaluation. Hepatic artery RI, portal vein diameter, portal vein velocity, splenic size, splenic vein diameter, and hepatic vein waveform were Doppler parameters measured. The study identified liver stiffness as being significantly related to hepatic parenchymal texture, splenic size, portal vein width, portal vein velocity and hepatic vein waveform changes. The portal vein velocities were decreased and hepatic artery resistive indexes were abnormal in a significant number of patients. The authors found Doppler ultrasound to be a valuable non-invasive tool for obtaining information on vascular changes of the liver in cirrhosis (38).

Using a longitudinal observational approach, Bevilacqua et al. (2024) examined the prognostic importance of porto-hepatic hemodynamics alteration in patients with cirrhosis in Italy. This study comprised 233 patients with cirrhosis and a median follow-up period of 24 months. The primary objective was to see if there was a relationship between non-forward portal flow (hepatofugal or abnormal direction of portal flow) and acute-on-chronic liver failure (ACLF) and liver-related death (LRD). The portal vein patency, portal flow direction and large portosystemic collaterals were assessed by color Doppler ultrasound. The study revealed that 56 patients developed acute-on-chronic liver failure, and 24 patients had baseline non-forward portal flow. Non-forward portal flow was an independent predictor of both acute-on-chronic liver failure and liver-related death, even after adjusting for age, etiology and disease severity scores. The study showed that the direction of portal flow was

important in advanced liver disease (39).

Azam et al. (2024) used a cross-sectional methodology in Pakistan to evaluate Doppler assessment of hepatic venous waveforms for predicting large esophageal varices in cirrhotic patients. The study was conducted at the Armed Forces Institute of Radiology and Imaging, Rawalpindi, and included 157 patients with liver cirrhosis. The aim was to determine the diagnostic accuracy of hepatic venous waveform analysis using esophagogastroduodenoscopy as the gold standard. Patients were classified according to Child-Pugh category, and Doppler ultrasound was performed with a 3.5–5 MHz convex probe. Hepatic venous waveforms were assessed and compared with endoscopic findings. The study found sensitivity of 93.33%, specificity of 94.0%, positive predictive value of 95.45%, negative predictive value of 91.30%, and diagnostic accuracy of 93.6% for predicting large esophageal varices. The authors concluded that Doppler waveform analysis is a useful non-invasive tool in cirrhosis assessment (40).

In a cross sectional survey study, Iqbal et al. (2024) compared PVV in liver cirrhosis patients divided into Child-Pugh categories in Lahore, Pakistan. The study was done at the Department of Diagnostic Radiology at Services Hospital Lahore with 70 patients of cirrhosis. Patients were classified as Child-Pugh score A, B or C and portal vein velocity was measured by ultrasound Doppler. The data were analyzed by SPSS 25 and analyzed using one-way ANOVA. The study revealed that mean portal vein flow velocity was significantly different by Child-Pugh group. Portal vein peak velocity decreased with the increase of Child-Pugh category, and reversed portal flow was seen in class C cirrhosis, and portal hemodynamics worsened with disease severity (41).

Based on liver biopsy and observational Doppler ultrasound methods, Tian et al. (2023) evaluated the Doppler parameters of the liver and portal veins in chronic hepatitis B patients with normal alanine transaminase levels in Chongqing, China. A total of 94 patients with chronic hepatitis B (cHBV) infection who had liver biopsy performed under ultrasound guidance were included in the

study. The primary objective was to assess if Doppler ultrasound of the hepatic vein and portal vein could aid identification of liver inflammation and fibrosis in the absence of elevated ALT levels. Patients were classified based on pathological liver tissue diagnosis and Doppler parameters were compared among the grades of inflammation and fibrosis. Liver sinusoidal Doppler parameters were different and significant in the patients with and without significant liver damage. The diameter of the portal vein increased with time as inflammation progressed and the blood flow velocity of the portal veins and superior mesenteric veins decreased. The study confirmed Doppler ultrasound as a useful non-invasive method to evaluate the haemodynamic changes in chronic HBV infection (42).

In this study, Malik et al. (2023) in Karachi, Pakistan assessed liver vein Doppler waveform patterns as a useful tool in the early identification of cirrhosis in HCV infected individuals using a cross-sectional prospective study design. This study was done in the Imaging Unit of the Radiology Department, Liaquat National Hospital for six months. All patients older than 20 and younger than 60 years with chronic HCV infection (more than 6 months), serologically confirmed by anti-HCV antibody by ELISA test, were included. A duplex sonographic scan of the hepatic veins was carried out and the waveforms were documented on a structured proforma. 114 of the 238 HCV-positive patients had Doppler waveform patterns consistent with cirrhosis (47.9%). The results indicated that use of Doppler waveform of the hepatic veins may provide an inexpensive method to identify non-invasively HCV-induced cirrhosis in chronic HCV patients (43).

In Japan, Yamaguchi et al. (2023) investigated the differences between portal vein hemodynamics and ultrasound elastography in the prediction of liver fibrosis in chronic liver disease via a single-arm retrospective study. Twenty-eight patients with chronic liver disease, including those with NAFLD, hepatitis B virus infection, and alcoholic liver disease were included in the study. To assess if portal vein flow velocity was a surrogate marker of liver stiffness/fibrosis. Transient elastography,

controlled attenuation parameter, two-dimensional shear-wave elastography, and attenuation imaging were used to evaluate liver stiffness and steatosis. Peak maximum velocity of right portal vein was measured using Doppler ultrasound. The study showed that there was an inverse correlation between liver stiffness and right portal vein velocity. A portal vein velocity cut-off of <17 cm/s was useful in detecting liver fibrosis, and the diagnostic accuracy was similar to that of the FIB-4 index. In chronic liver disease (44), portal vein velocity was emphasized as a useful hemodynamic indicator.

In Assiut, Egypt, Hassan et al. (2023) assessed hepatic fibrosis, portal hemodynamics and disease severity in HCV patients with liver cirrhosis following sustained virologic response (SVR) to direct-acting antiviral (DAA) drugs using a prospective longitudinal study design. 100 patients with chronic HCV-related cirrhosis were followed who received antiviral therapy. The goal was to determine if fibrosis and portal hemodynamics improved with viral eradication. Patients were assessed at the end of treatment (EOT), at 3-months and 12-months post-EOT. Assessment was performed by Doppler ultrasound of portal hemodynamics, shear wave elastography, APRI, FIB-4, Child-Pugh score and MELD score. The research revealed that fibrosis markers and liver stiffness were significantly decreased following treatment. There was also a significant improvement in Child-Pugh scores. After treatment, Doppler ultrasound revealed that the portal vein flow velocity was elevated and the time-average mean velocity and cross-sectional area of the portal vein were changed. The results indicated that HCV eradication could benefit portal hemodynamics in cirrhotic patients (45).

Retrospective clinical methodology was applied to explore the incidence of splenic artery steal syndrome in patients with hepatitis B-related cirrhosis, portal hypertension and hypersplenism in Nanchang, China by Mao et al (2023). Eighty-seven patients undergoing splenectomy and pericardial devascularization surgery were included in the study. The intention was to investigate the possibility of splenic artery steal

syndrome as a therapeutic target for the improvement of liver function and hepatic artery perfusion in decompensated cirrhosis. There were two groups: split patients into a splenic artery steal syndrome group and a control group based on the criteria, which included splenic artery enlargement, hepatic artery caliber, arterial flow and imaging findings. The study revealed that MELD score has improved following surgery, and hepatic artery diameter and hepatic artery velocity were significantly increased following treatment. The improvement was more in the splenic artery steal syndrome group. The study is relevant as it pointed out the importance of hepatic arterial perfusion change in HBV-related cirrhosis and the relevance of hepatic artery flow assessment (46).

Nouh et al. (2022) used a prospective case-control methodology in Egypt to assess the role of portal color Doppler ultrasonography as a non-invasive tool for predicting esophageal varices in cirrhotic patients. The study included 100 patients with liver cirrhosis and 100 healthy controls. The aim was to evaluate whether Doppler indices of the portal vein, hepatic artery, and splenic artery could help predict the presence of esophageal varices and reduce unnecessary endoscopic screening. Patients underwent clinical examination, laboratory assessment, upper gastrointestinal endoscopy, abdominal ultrasonography, and duplex Doppler assessment. Doppler parameters included portal vein diameter, portal vein flow velocity, portal congestion index, hepatic artery resistive index, hepatic artery pulsatility index, and splenic artery indices. The study found that portal vein diameter, portal vein flow velocity, portal congestion index, hepatic artery pulsatility index, and portal hypertensive index showed high sensitivity for predicting esophageal varices in cirrhotic patients (47).

Rana et al. (2022) used a cross-sectional methodology in New Delhi, India, to evaluate Doppler hemodynamic liver index and hepatic elastic modulus for non-invasive prediction of esophageal varices in cirrhotic patients. The study included 60 cirrhotic patients who underwent portal venous Doppler, liver sonoelastography, and upper gastrointestinal endoscopy within three

days of ultrasound assessment. The aim was to determine whether a combination of Doppler-based portal hypertension measurement and elastography-based fibrosis measurement could predict the presence and grade of esophageal varices. The Doppler hemodynamic liver index was calculated using portal vein diameter divided by mean portal vein velocity. The study found that patients with varices had significantly higher Doppler hemodynamic liver index values than those without varices. The index also increased with variceal grade, with the highest values observed in grade F3 varices. The study concluded that Doppler index combined with liver elasticity may reduce routine endoscopic screening (48).

In 2022, Onwuka et al. carried out a comparative Doppler ultrasound study in Nigeria to evaluate the hepatic venous waveform and mean maximum portal vein velocity in cirrhosis patients. A total of 60 patients with cirrhosis and 60 healthy controls of similar age and sex were included in the study. They wanted to assess the characteristics of hepatic venous waveform abnormality and portal vein velocity in relation to liver function status (measured by Child-Turcotte-Pugh classification). Hepatic venous waveform was classified as triphasic, biphasic or monophasic by Doppler ultrasound and mean maximum portal vein velocity was measured. The study revealed that 76.7% of cirrhotic patients had abnormal hepatic venous waveforms, and all of the controls had normal waveform patterns. Portal vein velocity was significantly decreased in the cirrhotic patients compared to the control. Hepatic venous waveform abnormality was correlating with Child-Turcotte-Pugh class significantly and there was no significant correlation between portal vein velocity and hepatic dysfunction (49).

In China, Cai et al. (2022) assessed the severity of PH by acoustic structure quantification analysis of liver parenchyma with non-invasive ultrasound methodology. There were 30 healthy matched controls and 60 patients with portal hypertension treated by surgical portosystemic shunting. The goal was to assess if ultrasound-based acoustic structure quantification would be an appropriate method to reflect portal pressure, GEV and liver

function. Hepatic ultrasonography, acoustic structure quantification, Doppler hepatic ultrasound, endoscopic examination, Child-Pugh classification, and intra-operative portal pressure measurement were performed for patients. Doppler parameters measured were portal vein velocity, hepatic artery resistive index (RI), splenic artery RI, and portal hypertension index (PHI). It was concluded that acoustic structure quantification parameters were significantly elevated in patients with portal hypertension and associated with the portal pressure, severity of varices and Doppler portal hypertension index. The results confirmed that ultrasound quantification could be a useful non-invasive marker of portal hypertensive changes in cirrhosis (50).

In Japan, Shigefuku et al. (2022) assessed the impacts of endoscopic injection sclerotherapy on portal hemodynamics and liver function with a prospective model of hepatic hemodynamic assessment in patients with esophagogastric varices and liver cirrhosis. Fifty-eight patients with cirrhosis secondary to hepatitis C, hepatitis B, alcohol, combined disease, non-alcoholic steatohepatitis and other causes were included in the study. The goal was to determine patients who would be appropriate for endoscopic injection sclerotherapy, based upon the assessment of PVTBF and HABF. Before and after treatment, portal venous tissue blood flow, hepatic arterial tissue blood flow and total hepatic tissue blood flow was measured with xenon enhanced computed tomography. Low indocyanine green retention, lack of paraesophageal veins and low portal-to-arterial blood flow ratio were found to be indicators of improvement in portal venous tissue blood flow in the study. There was also an improvement in the liver synthetic function after the treatment, which was correlated with the improved hepatic hemodynamics (51).

The authors of this study (Hui et al. 2021) explored the portal and splenic venous hemodynamics in liver cirrhosis patients in Shijiazhuang, China by retrospective color Doppler ultrasonography methodology. A total of 81 cirrhotic patients and 51 healthy volunteers

were included in the study. The goal was to evaluate whether the actual value of colour Doppler ultrasound for measuring parameters of portal vein and splenic vein and whether these parameters correlate with liver damage and esophageal varices could be demonstrated. The authors determined the diameter of the portal vein, portal vein velocity, portal vein flow volume, diameter of the splenic vein, splenic vein velocity, and splenic venous flow volume. The study reported portal vein diameter and portal vein flow volume to be elevated in the cirrhotic group while portal vein velocity and splenic vein diameter were found to be diminished compared to controls, and splenic vein flow volume was found to be unchanged. Doppler changes also became more prominent as Child-Pugh class and esophageal varices were worsened. This study confirms Doppler ultrasound as a helpful non invasive evaluation of cirrhotic hemodynamic disturbance (52).

To investigate the correlation between effective hepatic blood flow and liver pathology in hepatitis B virus-infected patients, Shu et al. (2021) employed a clinical observational approach in the city of Guangzhou, China. Two hundred seven patients with HBV infection were enrolled in the study, who had undergone liver biopsy and indocyanine green clearance tests. The purpose was to see if there was a correlation between the severity of hepatic inflammation and fibrosis based on effective hepatic blood flow. Liver biopsy results were graded based on Scheuer's scoring system and the effective hepatic blood flow was the result of the indocyanine green clearance test. It was observed that effective hepatic blood flow was significantly reduced with higher grades of inflammation and stages of fibrosis. It was inversely related to liver enzymes, APRI, FIB-4 and liver stiffness measurement. The authors suggested that the efficacy of hepatic blood flow may be able to assess pathological liver damage in HBV patients, and might be used to diagnose inflammation, fibrosis in the liver (53).

In the study by Chen et al., 2021, a retrospective clinical methodology was employed to evaluate the effective hepatic blood flow in acute-on-chronic

liver failure (ACLF) patients with hepatitis B virus (HBV) infection in Guangzhou, China. Patients with HBV related ACLF and decompensated cirrhosis underwent indocyanine green clearance testing in this study. The purpose was to assess the relationship between effective hepatic blood flow, disease severity and the prediction of 90-day mortality. Patients were divided into the following groups: ACLF (with cirrhosis), ACLF (without cirrhosis), and HBV-related decompensated cirrhosis. The study revealed a significant decrease in effective hepatic blood flow in ACLF patients as compared to decompensated cirrhosis patients. It was also strongly related to total bilirubin, prothrombin activity, and MELD score (54).

In Beijing, China, Wang et al. (2021) applied the imaging method of spectral computed tomography to evaluate the changes of hepatic parenchymal and vascular blood flow after transjugular intrahepatic portosystemic shunt (TIPS) in patients with liver cirrhosis caused by hepatitis B virus (HBV). Patients included in the study were 25 cirrhotics with HBV cirrhosis who had undergone TIPS for GEVB. To compare the iodine density of the liver parenchyma and vessels before and after TIPS as a non-invasive indicator of redistribution of hepatic blood flow. Contrast enhanced spectral CT (CE-SCT) was obtained before and within four weeks of TIPS in each patient. The study revealed that liver arterial iodine density fraction was significantly elevated after TIPS, indicating higher iodine supply to hepatic parenchymal perfusion by the arteries. There was an increase in portal vein iodine density after TIPS. Based on the above, the authors found that spectral CT iodine density could be used to effectively evaluate the changes in hepatic parenchymal and vascular flow in patients with HBV-related cirrhosis, without causing any lesions (55).

Zipprich et al. (2021) used a prospective proof-of-concept hemodynamic methodology in Germany to investigate the effect of selective endothelin-A receptor blockade on portal pressure and hepatic arterial perfusion in cirrhotic patients. The study included two substudies: local intrahepatic administration of BQ-123 and systemic oral

administration of ambrisentan. The aim was to determine whether blocking endothelin-A-mediated vasoconstriction could reduce portal pressure and alter hepatic arterial blood flow. Portal pressure was assessed using hepatic venous pressure gradient, while hepatic arterial blood flow was measured by intra-arterial Doppler in the local-administration substudy. The study found that endothelin-A blockade reduced hepatic venous pressure gradient and increased hepatic arterial blood flow. Non-responders in portal pressure reduction showed a higher increase in hepatic arterial flow. This study is relevant because it directly supports the role of vasoactive regulation in hepatic arterial perfusion in cirrhosis (56).

### Chapter 3

#### METHODOLOGY

##### 3.1 Research Design:

This study employed a cross-sectional analytical study design.

##### 3.2 Clinical Setting

The study was conducted in the Radiology Department of Farooq Hospital, Lahore.

##### 3.3 Duration

The study was conducted over a period of 3 months after synopsis approval.

##### 3.4 Sampling Technique:

A non-probability purposive sampling technique was employed.

##### 3.5 Sample Size Determination

The sample size was calculated using the single population proportion formula:

$$n = \frac{Z^2 \cdot P(1 - P)}{D^2}$$

Where:

Z = 1.96 (Z-score for 95% confidence level)

P = 0.049 (Estimated population proportion)

D = 0.055 (Margin of error)

$$n = \frac{(1.96)^2(0.049) \times (1 - 0.049)}{(0.055)^2}$$
$$n = \frac{0.1790}{0.00302}$$

$$n = 59.91$$

$$n \approx 60$$

Thus, a total of **6 patient records** included in the study.

##### 3.6 Inclusion Criteria

- Patients aged 18 years and above
- Diagnosed cases of chronic liver disease
- Patients with Hepatitis B (HBsAg positive) or Hepatitis C (Anti-HCV positive)
- Patients referred for abdominal Doppler ultrasound
- Patients willing to participate and providing written informed consent.

##### 3.7 Exclusion Criteria

- Patients with acute hepatitis
- Patients with alcoholic liver disease
- Patients with hepatic malignancy (hepatocellular carcinoma)
- Patients with portal vein thrombosis
- Patients with previous liver surgery or liver transplantation
- Patients with congestive cardiac failure or other cardiac conditions affecting hepatic blood flow
- Pregnant females.

##### 3.8 Data Collection Tool

###### 1. Structured Proforma:

A pre-designed proforma was used to record demographic data, clinical information, hepatitis status, and Doppler ultrasound findings.

###### 2. Doppler Ultrasound Machine:

Doppler ultrasound was used to assess portal vein and hepatic artery blood flow parameters non-invasively.

###### 3. Consent Form:

###### 4.

Written informed consent was obtained from all participants before inclusion in the study.

###### 5. Clinical Records:

###### 6.

Relevant clinical records were reviewed to confirm chronic liver disease and Hepatitis B or Hepatitis C status.

###### 7. Portal Vein Parameters:

Portal vein diameter, mean flow velocity, and flow direction were recorded through Doppler ultrasound.

## **8. Hepatic Artery Parameters:**

Hepatic artery peak systolic velocity, end diastolic velocity, resistive index, and pulsatility index were measured.

## **9. Hepatic Artery Buffer Response Assessment:**

Portal-vein and hepatic-artery Doppler parameters were evaluated as indirect markers of portal-arterial haemodynamic adaptation related to HABR. Direct dynamic HABR and volumetric hepatic arterial blood flow were not measured.

### **3.9 Data Collection Procedure**

After obtaining written informed consent, each eligible patient was received in the 07.0 Radiology Department of Farooq Hospital, Lahore and was assigned a unique identification code to maintain confidentiality. The demographic and clinical information, including age, gender, diagnosis of chronic liver disease, type of viral hepatitis, and relevant clinical history, was recorded on a pre-designed proforma. The hepatitis status was confirmed from available laboratory records, with Hepatitis B identified by HBsAg positivity and Hepatitis C identified by anti-HCV positivity. Patients were instructed to remain fasting for at least six hours before the Doppler examination to reduce bowel gas and improve visualization of hepatic vasculature. Each patient was examined in the supine position, and when required, slight left lateral positioning was used to improve the acoustic window. The examination was performed during quiet respiration or brief breath-holding to reduce motion-related Doppler artifacts.

Abdominal Doppler ultrasound was performed using a diagnostic ultrasound machine with color and spectral Doppler facility, model GE LOGIQ P9 / Toshiba Xario, equipped with a convex curvilinear transducer of approximately 2–5 MHz frequency. In soft tissue, this frequency range corresponds approximately to an ultrasound wavelength of 0.31–0.77 mm, depending on the selected frequency. B-mode scanning was first performed to assess liver size, liver parenchymal echotexture, surface regularity, splenic size, ascites, and gross hepatic morphology. Color Doppler was

then used to identify the main portal vein and hepatic artery at the porta hepatis. The Doppler angle was kept at 60 degrees or less to reduce velocity error, and the sample volume was adjusted according to vessel size, generally between 2–5 mm. Doppler gain, pulse repetition frequency, and wall filter were optimized to obtain a clear spectral waveform without aliasing or background noise.

The portal vein was evaluated at the main portal vein segment near the porta hepatis before its bifurcation. Portal vein diameter was measured in millimetres from inner wall to inner wall, and mean flow velocity was recorded in centimetres per second using pulsed-wave Doppler. Flow direction was documented as hepatopetal or hepatofugal. The hepatic artery was identified adjacent to the portal vein within the portal triad, and spectral Doppler waveforms were obtained from the proper or right hepatic artery. Hepatic artery peak systolic velocity, end diastolic velocity, resistive index, and pulsatility index were measured. The resistive index was calculated as PSV minus EDV divided by PSV. At least three acceptable waveforms were obtained, and the most stable reading or mean value was recorded. Hepatic artery buffer response was assessed indirectly by comparing portal vein flow parameters with hepatic artery Doppler parameters. All findings were entered into the structured proforma and later transferred to SPSS version 27.0 for statistical analysis.

### **3.10 Ethical Considerations**

Ethical approval for this study was obtained from the Institutional Review Board (IRB) of Superior University prior to data collection. Written informed consent were taken from the parents or guardians of all participants under 18 years of age, and assent were obtained from the child where appropriate. All patient data was handled confidentially, and identifiers such as names or hospital IDs were removed to maintain anonymity. Participation was voluntary, with the right to withdraw at any stage without penalty. The study was adhered to the guidelines of the

Declaration of Helsinki and maintain strict protection of patient privacy and clinical records.

### 3.11 Data Analysis

Data were analyzed using SPSS version 27.0. Each participant was assigned a coded identification number, and demographic, clinical, and Doppler ultrasound variables were entered into the software. Descriptive statistics were applied to summarize the data, where mean and standard deviation were calculated for quantitative variables such as age, portal vein diameter, portal vein velocity, hepatic artery peak systolic velocity, end diastolic velocity, resistive index, and pulsatility index. Frequencies and percentages were calculated for categorical variables such as gender, type of hepatitis, diagnosis of chronic liver disease, and portal vein flow direction. The normality of continuous variables was assessed before applying inferential tests. The independent sample t-test was used to compare normally distributed Doppler parameters between Hepatitis B and Hepatitis C patients, while the Mann-Whitney U test was applied for non-normally distributed variables. The chi-square test was used to assess associations between categorical variables. Pearson or Spearman correlation analysis was used to evaluate the relationship between portal vein parameters and hepatic artery Doppler parameters as indicators of hepatic artery buffer response. A p-value of  $\leq 0.05$  was considered statistically significant.

## Chapter 4

### 4.2 Demographic Information of Participants

#### 4.2.1 Age of Participants

**Table 4. 1: Frequency distribution of participants according to age group**

| Age group      | Frequency | Percent | Valid Percent | Cumulative Percent |
|----------------|-----------|---------|---------------|--------------------|
| 18–30 years    | 6         | 10.0    | 10.0          | 10.0               |
| 31–40 years    | 12        | 20.0    | 20.0          | 30.0               |
| 41–50 years    | 18        | 30.0    | 30.0          | 60.0               |
| 51–60 years    | 15        | 25.0    | 25.0          | 85.0               |
| Above 60 years | 9         | 15.0    | 15.0          | 100.0              |
| Total          | 60        | 100.0   | 100.0         |                    |

The age distribution indicated that most participants were middle-aged adults. The largest

## RESULTS

### 4.1 Results Summary

The study included 60 patients with chronic liver disease related to Hepatitis B or Hepatitis C. Most participants were aged between 31 and 60 years, with the 41–50-year group representing the largest proportion. Male participants accounted for 60.0% of the sample, while females represented 40.0%. Hepatitis C was more common than Hepatitis B, accounting for 63.3% and 36.7% of cases, respectively. Descriptive analysis showed a mean liver length of 15.82 cm and a mean splenic length of 13.48 cm. The mean portal vein diameter was 13.16 mm, while the mean portal vein flow velocity was 15.62 cm/s.

Comparative analysis showed that HCV patients had a lower mean portal vein flow velocity than HBV patients (14.94 vs 16.80 cm/s). In contrast, HCV patients demonstrated higher hepatic artery peak systolic velocity (49.01 vs 44.52 cm/s), resistive index (0.72 vs 0.66), and pulsatility index (1.37 vs 1.23). Significant differences were identified in portal vein velocity, hepatic artery PSV, RI, and PI, while EDV did not differ significantly between the two groups. Correlation analysis further showed that portal vein flow velocity was significantly and negatively associated with hepatic artery PSV, RI, and PI. Overall, the findings indicated greater portal–arterial haemodynamic alteration among HCV patients and supported the presence of compensatory hepatic arterial changes in response to reduced portal venous flow.

group comprised participants aged 41–50 years, representing 30.0% of the sample. Participants aged 51–60 years constituted 25.0%, while 20.0% were aged 31–40 years. Individuals aged above 60 years accounted for 15.0%, whereas participants aged 18–30 years represented the smallest age category at 10.0%. The cumulative distribution demonstrated that 60.0% of participants were

aged 50 years or younger, while 85.0% were aged 60 years or younger. Overall, 75.0% of the participants were between 31 and 60 years of age, indicating that the study population was predominantly composed of middle-aged patients with Hepatitis B- or Hepatitis C-related chronic liver disease.

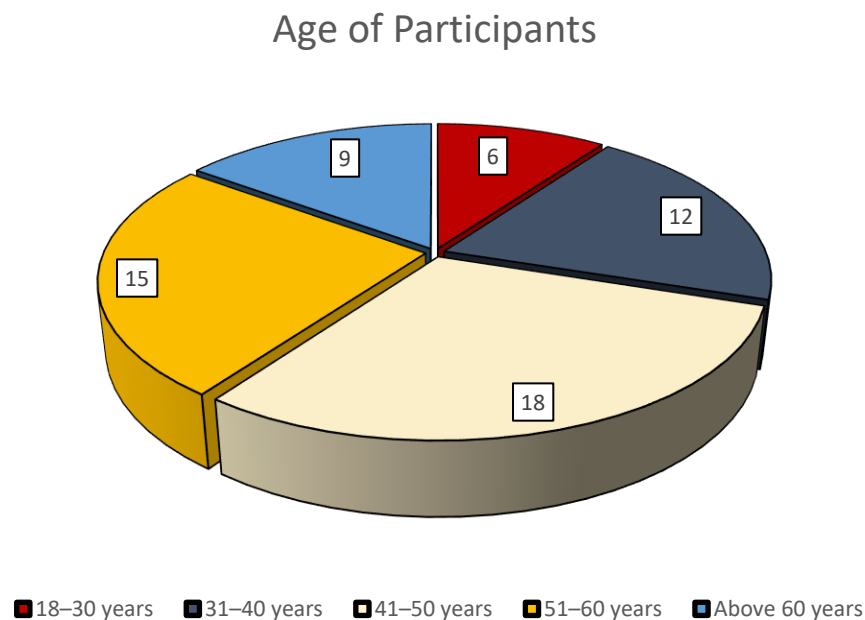


Figure 4. 1: Participants aged 41–50 years formed the largest age group, accounting for 30.0% of the sample, followed by those aged 51–60 years at 25.0%.

#### 4.2.2 Gender Distribution of Participants

Table 4. 2: Frequency distribution of participants according to gender

| Gender | Frequency | Percent | Valid Percent | Cumulative Percent |
|--------|-----------|---------|---------------|--------------------|
| Male   | 36        | 60.0    | 60.0          | 60.0               |
| Female | 24        | 40.0    | 40.0          | 100.0              |
| Total  | 60        | 100.0   | 100.0         |                    |

The gender distribution revealed a higher representation of male participants than female participants. Of the 60 chronic liver disease patients included in the study, 36 were male, accounting for 60.0% of the sample, whereas 24 were female, representing 40.0%. The valid percentages were identical to the overall percentages because no missing gender data were

assumed in the dataset. The difference between male and female participation was 20 percentage points, with 12 more males than females. This distribution indicates a moderate male predominance within the selected study population. However, the finding describes only the demographic composition of the current sample and should not be interpreted as evidence

that chronic viral liver disease is universally more prevalent among males without further

population-based analysis.

Gender Distribution of Participants

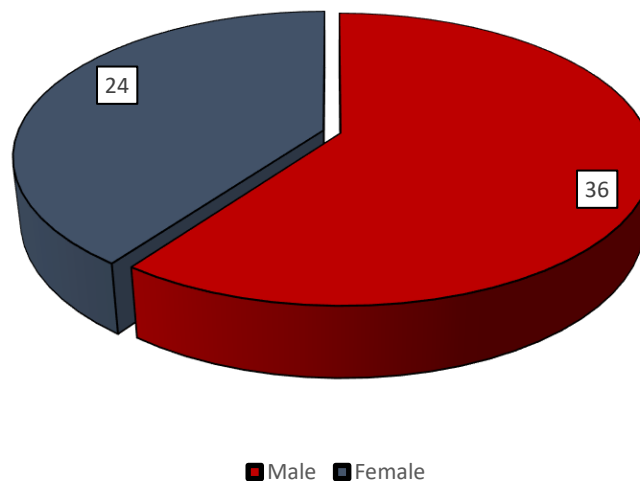


Figure 4. 2: Male participants constituted 60.0% of the study population, whereas female participants represented the remaining 40.0%.

#### 4.2.3 Distribution According to Viral Hepatitis Type

Table 4. 3: Frequency distribution of participants according to viral hepatitis type

| Valid viral hepatitis type | Frequency | Percent      | Valid Percent | Cumulative Percent |
|----------------------------|-----------|--------------|---------------|--------------------|
| Hepatitis B                | 22        | 36.7         | 36.7          | 36.7               |
| Hepatitis C                | 38        | 63.3         | 63.3          | 100.0              |
| <b>Total</b>               | <b>60</b> | <b>100.0</b> | <b>100.0</b>  |                    |

The distribution according to viral hepatitis type indicated that Hepatitis C was more frequently represented than Hepatitis B. Among the 60 participants, 38 were diagnosed with Hepatitis C, accounting for 63.3% of the sample, while 22 had Hepatitis B, representing 36.7%. The Hepatitis C group therefore exceeded the Hepatitis B group by 16 participants and 26.6 percentage points. All cases had a recorded viral hepatitis diagnosis;

therefore, the percent and valid-percent values were identical. Although the two groups were unequal in size, both contained a reasonable number of participants for comparing portal vein measurements, hepatic artery Doppler parameters and hepatic artery buffer response indicators. The results suggest that HCV-related chronic liver disease was more frequently encountered in the study sample than HBV-related disease.

Distribution According to Viral Hepatitis Type

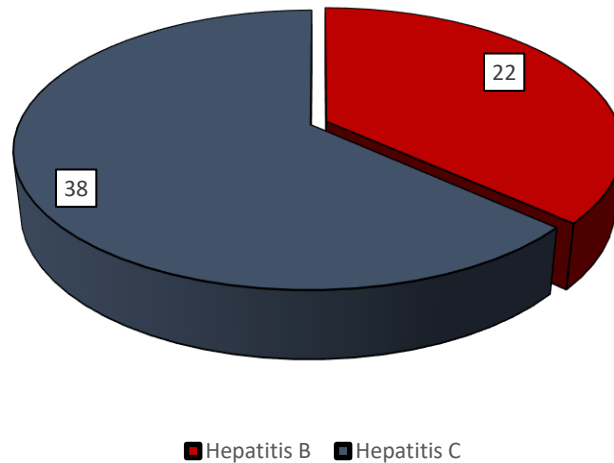


Figure 4. 3: Hepatitis C represented the predominant viral etiology, accounting for 63.3% of participants, while Hepatitis B accounted for 36.7%.

#### 4.3 Clinical and Doppler Ultrasound Characteristics

##### 4.3.1 Descriptive Statistics of Liver and Splenic Measurements

The results of descriptive analysis of the liver organ measurement revealed that the mean liver length of the participants was 15.82 cm. The median liver length was 15.70 cm and the most frequently recorded liver length was 15.50 cm. The values for the mean, median and mode were fairly close

together, indicating that the length of the liver was reasonably concentrated around the average, or mean. Moderate variation was indicated by the following results: The standard deviation was 1.36 cm and the variance was 1.85. Splenic length had slightly more standard deviation (1.52 cm) and variance (2.31) than liver length, indicating that it was slightly more variable. The measurements summarize liver and spleen size distribution of the study sample.

Table 4. 4: Descriptive statistics of liver and splenic measurements among the participants. .

| Measurement         | Mean  | Mode  | Median | Standard Deviation | Variance |
|---------------------|-------|-------|--------|--------------------|----------|
| Liver length (cm)   | 15.82 | 15.50 | 15.70  | 1.36               | 1.85     |
| Splenic length (cm) | 13.48 | 13.00 | 13.30  | 1.52               | 2.31     |

##### 4.3.2 Descriptive Statistics of Portal Vein Doppler Parameters

Portal vein Doppler characteristics were measured in terms of diameter of portal vein and mean velocity of flow. The diameter of the portal vein measured in mean, median and mode was 13.16 mm, 13.00 mm and 12.80 mm respectively. The relatively small range between these measures of central tendency showed that the diameter of the

portal veins was fairly distributed. The variance was 2.07 and the standard deviation was 1.44 mm. The mean flow velocity of portal vein was 15.62 cm/s, the median 15.40 cm/s and the mode was 15.00 cm/s. There was more variation in portal vein velocity with a standard deviation of 3.12 cm/s and variance of 9.73. The findings suggest that there was greater difference in flow velocity between participants than portal vein diameter.

Table 4. 5: Descriptive statistics of Doppler parameters of portal vein in the participants. The mean value of portal vein diameter (PVD) was  $13.16 \pm 1.44$  mm and portal vein mean flow

velocity was  $15.62 \pm 3.12$  cm/s. The diameter data had a lower standard deviation and lower variance when compared to the flow velocity data indicating greater dispersion in flow velocity.

**Table 4. 5: Descriptive statistics of portal vein Doppler parameters among the participants. Portal vein diameter averaged  $13.16 \pm 1.44$  mm, while portal vein mean flow velocity averaged  $15.62 \pm 3.12$  cm/s.**

| Portal vein parameter                 | Mean  | Mode  | Median | Standard Deviation | Variance |
|---------------------------------------|-------|-------|--------|--------------------|----------|
| Portal vein diameter (mm)             | 13.16 | 12.80 | 13.00  | 1.44               | 2.07     |
| Portal vein mean flow velocity (cm/s) | 15.62 | 15.00 | 15.40  | 3.12               | 9.73     |

#### 4.3.3 Descriptive Statistics of Hepatic Artery Doppler Parameters

Doppler parameters of the hepatic artery were peak systolic velocity (PSV), end-diastolic velocity (EDV), the resistive index (RI), and the pulsatility index (PI). The mean peak systolic velocity was 47.36 cm/s, the median was 46.90 cm/s and the mode was 45.00 cm/s. The standard deviation of its results was 8.42 cm/s, meaning that there was

some variation between participants. The mean end-diastolic velocity was 14.28 cm/s, the median velocity was 14.00 cm/s and the mode velocity was 13.50 cm/s. The mean RI of the hepatic artery was  $0.70 \pm 0.08$ . The mean of the pulsatility index was 1.32 with a standard deviation (SD) of 0.21. In total, the peak systolic velocity had the highest absolute difference in values, and the RI had the lowest difference in values.

**Table 4. 6: Descriptive statistics of hepatic artery Doppler parameters among the participants.**

| Hepatic artery parameter      | Mean  | Mode  | Median | Standard Deviation | Variance |
|-------------------------------|-------|-------|--------|--------------------|----------|
| Peak systolic velocity (cm/s) | 47.36 | 45.00 | 46.90  | 8.42               | 70.90    |
| End-diastolic velocity (cm/s) | 14.28 | 13.50 | 14.00  | 3.21               | 10.30    |
| Resistive index               | 0.70  | 0.69  | 0.70   | 0.08               | 0.0064   |
| Pulsatility index             | 1.32  | 1.28  | 1.30   | 0.21               | 0.0441   |

#### 4.4 Comparison of Hepatic Artery Buffer Response Between HBV and HCV Patients

Comparisons of HABR quantifiers showed significant differences between Hepatitis B and C patients in describing the response. The mean portal vein flow velocity was lower in the HCV group than in the HBV group (14.94 and 16.80 cm/s, respectively). On the other hand, patients with HCV had higher peak systolic velocity of hepatic arteries (49.01 cm/s) than those with HBV

(44.52 cm/s). Even higher were the mean hepatic artery RI and PI in the HCV group. HBV patients had slightly higher end diastolic velocity. Overall, the lower portal venous velocity and higher hepatic arterial values in the HCV group indicated a comparatively larger change in portal-arterial blood-flow compensation. HABR is determined by compensatory hepatic arterial velocity and resistance changes when portal venous flow is decreased.

**Table 4. 7: Comparison of hepatic artery buffer response indicators between HBV and HCV patients.**

| HABR indicator                        | HBV patients, n = 22<br>Mean $\pm$ SD | HCV patients, n = 38<br>Mean $\pm$ SD | Mean difference (HBV – HCV) |
|---------------------------------------|---------------------------------------|---------------------------------------|-----------------------------|
| Portal vein mean flow velocity (cm/s) | $16.80 \pm 2.74$                      | $14.94 \pm 3.20$                      | 1.86                        |
| Hepatic artery PSV (cm/s)             | $44.52 \pm 7.35$                      | $49.01 \pm 8.55$                      | -4.49                       |
| Hepatic artery EDV                    | $14.78 \pm 2.88$                      | $14.00 \pm 3.37$                      | 0.78                        |

|                                  |                 |                 |       |
|----------------------------------|-----------------|-----------------|-------|
| (cm/s)                           |                 |                 |       |
| Hepatic artery resistive index   | $0.66 \pm 0.07$ | $0.72 \pm 0.08$ | -0.06 |
| Hepatic artery pulsatility index | $1.23 \pm 0.18$ | $1.37 \pm 0.22$ | -0.14 |

Collectively, these results suggested that HCV patients had a more abnormal hepatic artery buffer response than HBV patients. A smaller proportion of HCV patients had a decreased or abnormal compensatory response (73.7% compared with 45.5% for HBV). Furthermore, 80.0% (12/15 patients) of those classified as

having impaired HABR were in the HCV group. This is similar to the findings of lower Portal vein velocity and higher Hepatic artery PSV, resistive index and pulsatility index seen in HCV patients. However, these results are only descriptive comparisons.

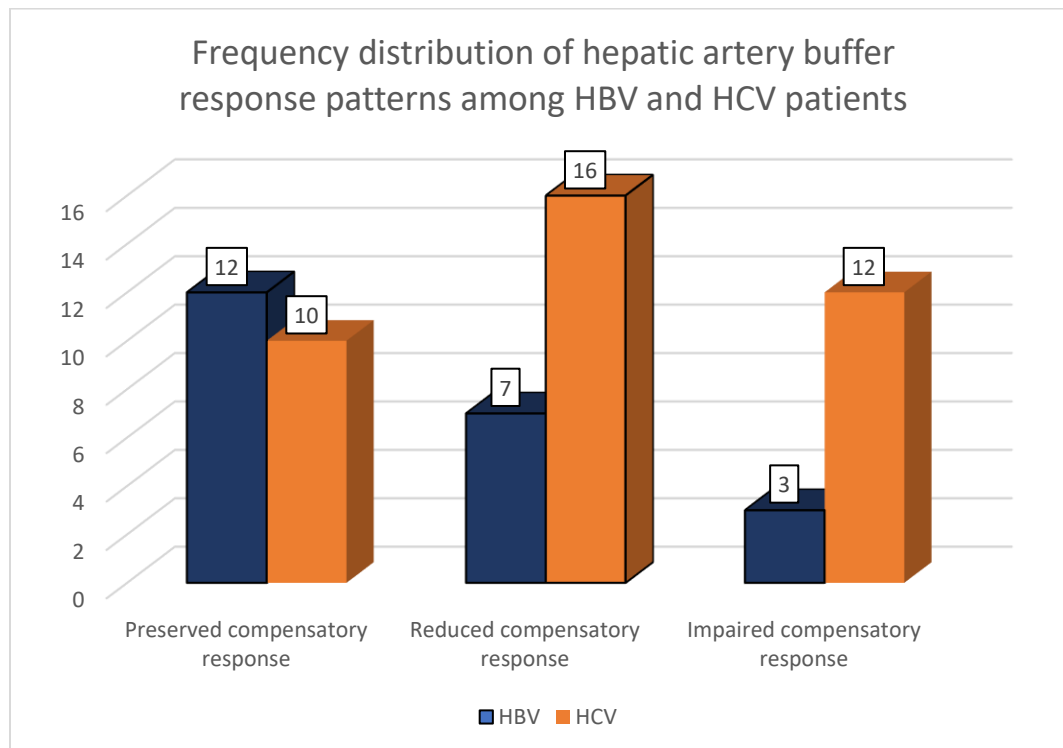


Figure 4. 4: Preserved hepatic arterial compensation was observed in 54.5% of HBV patients but only 26.3% of HCV patients.

#### 4.5 Comparison of Portal Vein Parameters Between HBV and HCV Patients

Doppler parameters of the portal vein were compared descriptively with regard to the cause of liver disease, and the differences were observed between the two groups: Hepatitis B patients and Hepatitis C patients. The mean portal vein diameter of the HCV group was larger than that of the HBV group (13.48 mm and 12.62 mm,

respectively). By contrast, mean portal vein flow velocity was reduced in HCV patients (mean 14.94 cm/s) compared to mean 16.80 cm/s in patients with HBV. The mean diameter of the portal vein in the two groups was 0.86 mm apart, and the flow velocity was 1.86 cm/s apart. Based on the results, it can be inferred that the portal vein dilatation was higher and portal venous flow lower in HCV patients as compared to the other groups. The

main portal venous measurements obtained by Doppler ultrasound in the study were portal vein

diameter, mean velocity and flow direction.

Table 4. 8: Descriptive comparison of portal vein Doppler parameters between patients with Hepatitis B and Hepatitis C.

| Portal vein parameter                 | HBV patients, n = 22<br>Mean $\pm$ SD | HCV patients, n = 38<br>Mean $\pm$ SD | Mean difference (HCV – HBV) |
|---------------------------------------|---------------------------------------|---------------------------------------|-----------------------------|
| Portal vein diameter (mm)             | 12.62 $\pm$ 1.21                      | 13.48 $\pm$ 1.49                      | 0.86                        |
| Portal vein mean flow velocity (cm/s) | 16.80 $\pm$ 2.74                      | 14.94 $\pm$ 3.20                      | -1.86                       |

The overall results showed more severe haemodynamic alterations in the portal vein in HCV patients as compared to the other groups. Hepatopetal flow was still the predominant flow in both groups, but 9/11 of those with hepatofugal flow were in the HCV group. That made the number of HCV patients 81.8% of all hepatofugal cases in the sample. The mean diameter of portal veins and mean flow velocity were also higher in the HCV group than the HBV group. The results

could indicate that patients with chronic liver disease due to HCV have higher portal venous resistance or more advanced disruption of normal hepatic blood flow. The differences are descriptive and do not imply statistical significance, however; and the proper inferential tests will have to confirm if the hepatitis type is significantly associated with the Doppler parameters of the portal vein.

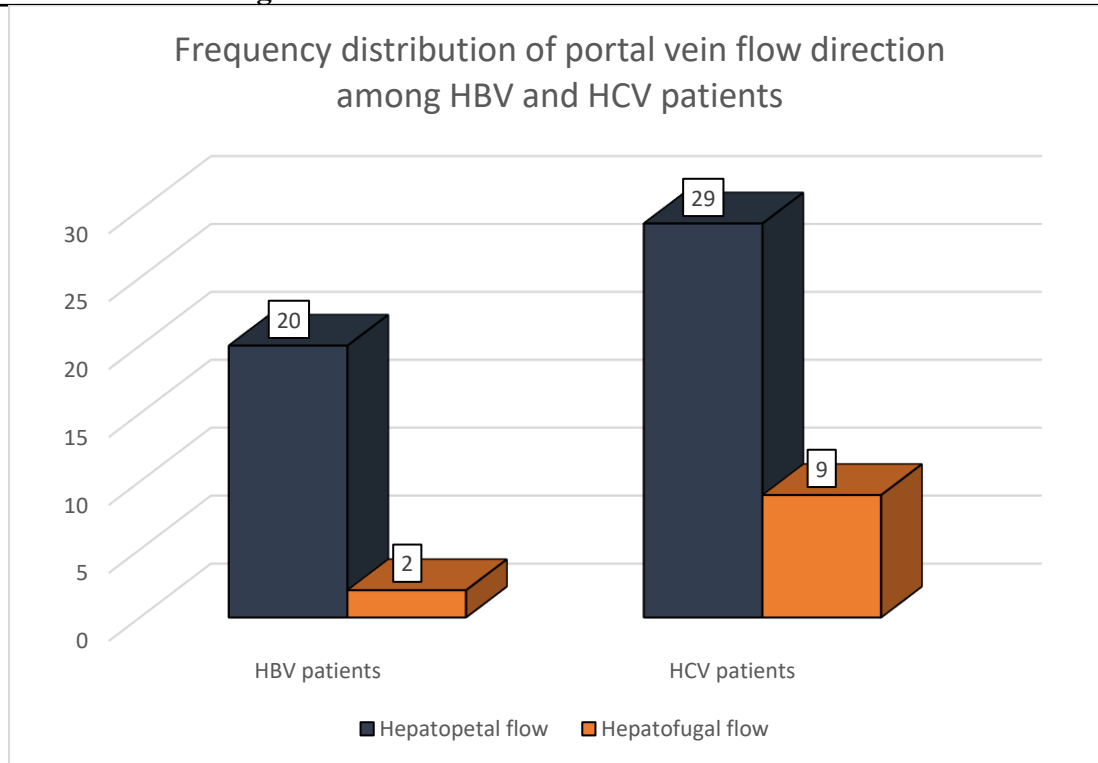


Figure 4. 5: Hepatopetal flow remained the predominant portal vein flow direction in both diagnostic groups, occurring in 20 HBV patients and 29 HCV patients.

#### 4.6 Comparison of Hepatic Artery Parameters Between HBV and HCV Patients

Patients with Hepatitis B and Hepatitis C had a difference in mean peak systolic velocity with HCV group having a higher velocity of 49.01 cm/s whereas the HBV group had a velocity of 44.52 cm/s, giving a difference of 4.49 cm/s. HCV patients had slightly lower mean end-diastolic velocity of 14.00 cm/s compared to HBV patients

of 14.78 cm/s. Mean hepatic artery resistance index was 0.72 in HCV and 0.66 in HBV patients, whereas the mean PI values were 1.37 and 1.23, respectively. The higher PSV, RI and PI in the HCV group together suggested a greater change in the blood flow and vascular resistance of the hepatic artery. The main arterial Doppler parameters recorded on the study proforma are hepatic artery PSV, EDV, RI and PI.

Table 4. 9: Descriptive comparison of hepatic artery Doppler parameters between patients with Hepatitis B and Hepatitis C.

| Hepatic artery parameter      | HBV patients, n = 22<br>Mean $\pm$ SD | HCV patients, n = 38<br>Mean $\pm$ SD | Mean difference (HCV – HBV) |
|-------------------------------|---------------------------------------|---------------------------------------|-----------------------------|
| Peak systolic velocity (cm/s) | 44.52 $\pm$ 7.35                      | 49.01 $\pm$ 8.55                      | 4.49                        |
| End-diastolic velocity (cm/s) | 14.78 $\pm$ 2.88                      | 14.00 $\pm$ 3.37                      | -0.78                       |
| Resistive index               | 0.66 $\pm$ 0.07                       | 0.72 $\pm$ 0.08                       | 0.06                        |
| Pulsatility index             | 1.23 $\pm$ 0.18                       | 1.37 $\pm$ 0.22                       | 0.14                        |

In summary, the findings of the hepatic artery

indicated that HCV patients had more hepatic

artery haemodynamic alteration than HBV patients. Twenty-four HCV subjects accounted for 77.4% of those with a RI value of 0.70 or more (31 subjects total). The majority of HBV patients, however, had an RI value less than 0.70. These were further confirmed by the increased mean PSV and PI in the HCV group. At the same time,

EDV was slightly reduced in HCV patients which resulted in higher calculated RI. These descriptive results suggest that HCV patients had more altered arterial blood flow in the liver, but statistical significance of the difference between the two groups will need to be determined by inferential analysis.

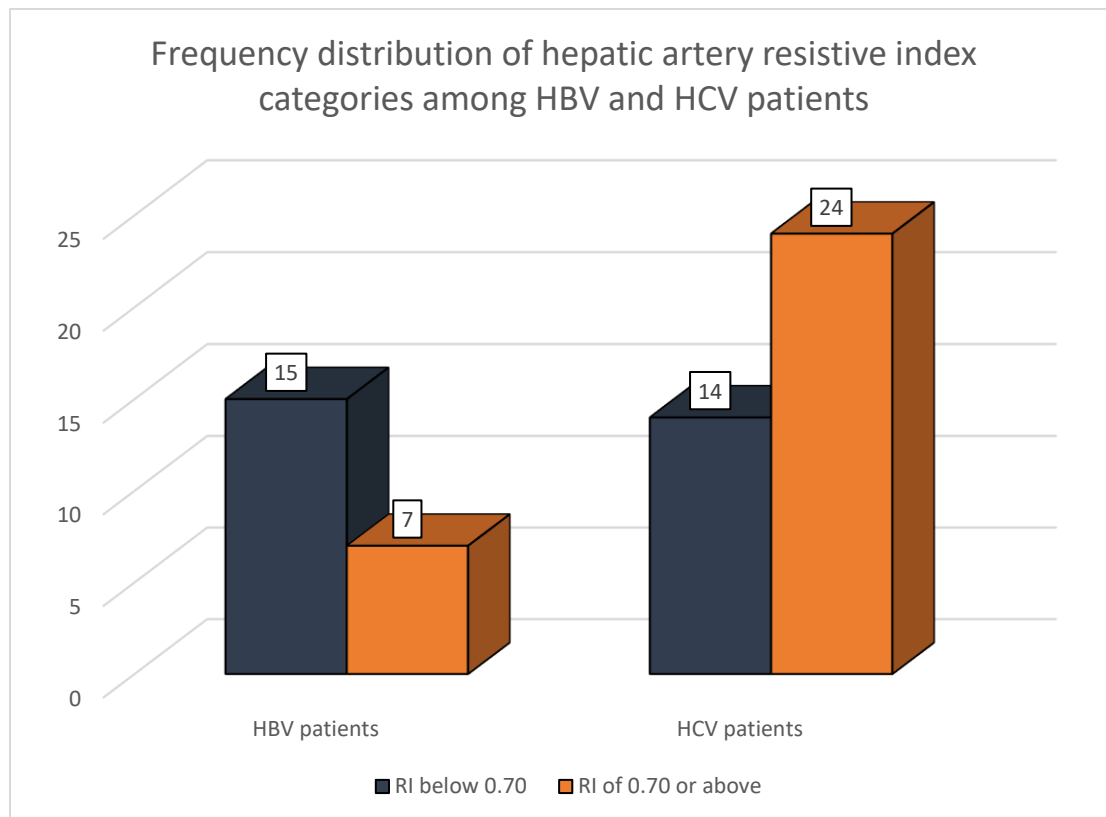


Figure 4. 6: An RI of 0.70 or above was recorded in 24 HCV patients compared with 7 HBV patients, whereas values below 0.70 occurred in 15 HBV and 14 HCV patients.

#### 4.7 Hypothesis 1 Testing: Difference in Hepatic Artery Buffer Response Between HBV and HCV Patients

- **Null hypothesis ( $H_{01}$ ):** There is no significant difference in hepatic artery buffer response between chronic liver disease patients with Hepatitis B and Hepatitis C.

- **Alternative hypothesis ( $H_{11}$ ):** There is a significant difference in hepatic artery buffer response between chronic liver disease patients with Hepatitis B and Hepatitis C.

An independent-samples t-test was used to compare the Doppler indicators of HBV and

HCV group regarding the HABR. The HCV group showed significantly lower PV-MFV and higher HA-PSV, RI and PI than the HBV group. The results of the Levene's test were all  $> 0.05$ , which meant that the assumption of equal variances was not violated. The "equal variances assumed" rows are used to interpret the results, therefore. The portal vein velocity, hepatic artery PSV as well as RI and PI were significantly different between the groups, while the difference in hepatic artery EDV was not significant. The hepatic arterial changes caused by decreased portal venous flow were used to evaluate HABR.

**Table 4. 10: Group Statistics**

| HABR indicator                        | Viral hepatitis type | N  | Mean   | Std. Deviation | Std. Error |
|---------------------------------------|----------------------|----|--------|----------------|------------|
| Portal vein mean flow velocity (cm/s) | HBV                  | 22 | 16.800 | 2.740          | 0.584      |
|                                       | HCV                  | 38 | 14.940 | 3.200          | 0.519      |
| Hepatic artery PSV (cm/s)             | HBV                  | 22 | 44.520 | 7.350          | 1.567      |
|                                       | HCV                  | 38 | 49.010 | 8.550          | 1.387      |
| Hepatic artery EDV (cm/s)             | HBV                  | 22 | 14.780 | 2.880          | 0.614      |
|                                       | HCV                  | 38 | 14.000 | 3.370          | 0.547      |
| Hepatic artery resistive index        | HBV                  | 22 | 0.660  | 0.070          | 0.015      |
|                                       | HCV                  | 38 | 0.720  | 0.080          | 0.013      |
| Hepatic artery pulsatility index      | HBV                  | 22 | 1.230  | 0.180          | 0.038      |
|                                       | HCV                  | 38 | 1.370  | 0.220          | 0.036      |

**Table 4. 11: Independent Samples Test**

| HABR indicator                 | Variance assumption         | Levene's F | Sig.  | t      | df     | Sig. (2-tailed) | Mean Difference | Std. Error Difference | 95% CI Lower | 95% CI Upper |
|--------------------------------|-----------------------------|------------|-------|--------|--------|-----------------|-----------------|-----------------------|--------------|--------------|
| Portal vein mean flow velocity | Equal variances assumed     | 0.412      | 0.524 | 2.283  | 58     | 0.026           | 1.860           | 0.815                 | 0.229        | 3.491        |
|                                | Equal variances not assumed |            |       | 2.380  | 49.678 | 0.021           | 1.860           | 0.781                 | 0.290        | 3.430        |
| Hepatic artery PSV             | Equal variances assumed     | 0.681      | 0.413 | -2.060 | 58     | 0.044           | -4.490          | 2.180                 | -8.853       | -0.127       |
|                                | Equal variances not assumed |            |       | -2.146 | 49.537 | 0.037           | -4.490          | 2.093                 | -8.694       | -0.286       |
| Hepatic artery EDV             | Equal variances assumed     | 0.295      | 0.589 | 0.909  | 58     | 0.367           | 0.780           | 0.858                 | -0.937       | 2.497        |
|                                | Equal variances not assumed |            |       | 0.949  | 49.747 | 0.347           | 0.780           | 0.822                 | -0.871       | 2.431        |
| Hepatic artery resistive       | Equal variances assumed     | 1.214      | 0.275 | -2.926 | 58     | 0.005           | -0.060          | 0.021                 | -0.101       | -0.019       |

|                                            |                                      |       |           |            |            |           |        |       |            |            |
|--------------------------------------------|--------------------------------------|-------|-----------|------------|------------|-----------|--------|-------|------------|------------|
| index                                      |                                      |       |           |            |            |           |        |       |            |            |
|                                            | Equal<br>variances<br>not<br>assumed |       |           | -3.03<br>4 | 48.89<br>8 | 0.00<br>4 | -0.060 | 0.020 | -0.10<br>0 | -0.02<br>0 |
| Hepatic<br>artery<br>pulsatili<br>ty index | Equal<br>variances<br>assumed        | 0.844 | 0.36<br>2 | -2.53<br>2 | 58         | 0.01<br>4 | -0.140 | 0.055 | -0.25<br>1 | -0.02<br>9 |
|                                            | Equal<br>variances<br>not<br>assumed |       |           | -2.67<br>1 | 51.26<br>7 | 0.01<br>0 | -0.140 | 0.052 | -0.24<br>5 | -0.03<br>5 |

The alternative hypothesis was supported as four of the five Doppler indicators showed statistically significant differences in the two viral-hepatitis groups. The mean flow velocity of the portal vein was significantly elevated in HBV patients while the PSV, RI and PI of the hepatic artery were significantly elevated in HCV patients. Significant between-group differences were observed in portal-vein mean flow velocity, hepatic-artery PSV, RI and PI, whereas hepatic-artery EDV did not differ significantly between the HBV and HCV groups. These findings demonstrate differences in the portal-arterial Doppler haemodynamic profile of the two groups.

#### 4.8 Hypothesis 2 Testing: Relationship Between Portal Vein Flow and Hepatic Arterial Compensation

- **Null hypothesis (H<sub>02</sub>):** There is no significant relationship between portal vein mean flow velocity and hepatic artery Doppler parameters among patients with chronic liver disease.

- **Alternative hypothesis (H<sub>12</sub>):** There is a significant relationship between portal vein mean flow velocity and hepatic artery Doppler parameters among patients with chronic liver disease.

Pearson's product-moment correlation was used to assess the correlation between PV MV and the Doppler parameters of peak systolic velocity, end-diastolic velocity, RI and PI in the hepatic artery. The analysis was based on all 60 participants. The hepatic artery PSV and RI and the hepatic artery PI had significant negative correlation with portal vein flow velocity. This suggested that there was a correlation between low portal venous velocity and high hepatic arterial velocity and vascular-resistance values. The correlation between portal vein flow velocity and hepatic artery EDV was however weak and not significant. This analysis directly assesses the physiological basis of HABR, which is referred to as the "hygiene hypothesis. This analysis directly tests the physiological principle of HABR.

Table 4. 12: Descriptive Statistics

| Study variable                        | Mean  | Std. Deviation | N  |
|---------------------------------------|-------|----------------|----|
| Portal vein mean flow velocity (cm/s) | 15.62 | 3.12           | 60 |
| Hepatic artery PSV (cm/s)             | 47.36 | 8.42           | 60 |
| Hepatic artery EDV (cm/s)             | 14.28 | 3.21           | 60 |

|                                  |      |      |    |
|----------------------------------|------|------|----|
| Hepatic artery resistive index   | 0.70 | 0.08 | 60 |
| Hepatic artery pulsatility index | 1.32 | 0.21 | 60 |

Table 4. 13: Correlations

|                                |                     | Hepatic artery PSV | Hepatic artery EDV | Hepatic artery RI | Hepatic artery PI |
|--------------------------------|---------------------|--------------------|--------------------|-------------------|-------------------|
| Portal vein mean flow velocity | Pearson Correlation | -0.463**           | 0.182              | -0.512**          | -0.421**          |
|                                | Sig. (2-tailed)     | <0.001             | 0.164              | <0.001            | 0.001             |
|                                | N                   | 60                 | 60                 | 60                | 60                |

\*\* Correlation is significant at the 0.01 level (2-tailed).

The results of the correlation analysis were in favor of the alternative hypothesis. There was a moderate negative correlation between mean velocity of the portal vein and PSV of hepatic artery ( $r = -0.463$ ,  $p < 0.001$ ), suggesting that lower portal venous velocity was linked to higher hepatic arterial PSV. The best correlation was found between hepatic artery RI and portal vein velocity ( $r = -0.512$ ,  $p < 0.001$ ). The hepatic artery PI was also significantly negatively correlated with area ( $r = -0.421$ ,  $p = 0.001$ ). The correlation with EDV, on the other hand, was not significant,  $r = 0.182$ ,  $p = 0.164$ . The results revealed that there were significant relationships between the three of the four hepatic artery parameters and portal vein velocity, therefore the null hypothesis was rejected and the alternative hypothesis was accepted. The findings are consistent with the presence of hepatic arterial compensation to portal venous hyp perfusion.

## Chapter 5

### DISCUSSION

In the present study, the relationship between hepatic artery buffer response (HABR) and chronic liver disease from the Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) was investigated with the Doppler parameters of the portal vein (PV) and hepatic artery (HA). Most of the participants were in the age group of 41 to 50 years, with majority of cases male (60.0%), and those with HCV-related chronic liver disease

(63.3%). A coarse appearance of the liver parenchyma was also the most common ultrasound finding. The findings indicate that most of the patients were those with long-standing structural liver alterations. The demographic distribution, however, is not a population level estimate of the prevalence of HBV or HCV, but rather represents those patients who were included with the selected hospital. Main study goals were examining Doppler parameters of portal and hepatic artery as well as the correlation of these parameters with viral hepatitis type.

Some of the organ measurements also were descriptive, indicating chronic hepatic and portal-system changes. The mean length of the liver was 15.82 cm and splenic mean length was 13.48 cm with more variation in the size of the spleen. Portal hypertension may be associated with splenic enlargement due to increased resistance in portal circulation which can impact splenic venous drainage. However, liver and spleen measurements are not enough to assess the severity of portal hypertension or differentiate the HBV-related disease from the HCV-related disease. Therefore, functional Doppler measurements are also of importance in addition to anatomy. In a recent study by Alempijevic et al. (2017), it was concluded that Doppler ultrasound was useful for evaluating liver fibrosis when used in conjunction with other clinical and imaging parameters, which is why using more than one parameter is preferable over single parameters (57).

The most important result of the study was that of the HCV patients showed a more distorted

pattern of hepatic arterial compensation compared to the HBV patients. The hepatic-artery peak systolic velocity, resistive index and pulsatility index were higher, whereas the portal-vein flow velocity was lower, in the HCV group. Additionally, reduced/impaired HABR was more common in the HCV patients. This pattern is similar to the physiology of HABR (hepatic arterial blood flow compensation) in which a decrease in the portal venous contribution is associated with a compensatory increase in hepatic arterial flow. The synopsis also describes HABR as a compensatory change in hepatic arterial flow and resistance seen in response to decreased portal venous flow. Walsh et al (1998) also found higher hepatic arterial blood flow and Doppler perfusion index in chronic Hepatitis C patients than healthy persons. They did not find a definite association between these indices and histological severity, however, so that changes in blood flow does not necessarily correspond directly to the stage of fibrosis (58).

The comparison of portal-vein parameters showed that the portal-vein diameter, portal-vein flow velocity and hepatofugal flow were more in the HCV patients than in the HBV patients. A lower portal velocity may be a consequence of higher intrahepatic resistance, due to fibrosis and architectural distortion, and sinusoidal remodelling. In patients with chronic Hepatitis C, Ikeda et al. (2007) reported that portal venous tissue blood flow was significantly reduced as fibrosis proceeded, which is consistent with the reduced portal-flow in the present HCV group (59). Soker et al (2016) also concluded that portal velocity or hepatic arterial indices may aid in the separation of cirrhotic from non-cirrhotic viral Hepatitis B and C patients. The authors however, pointed out that unlike other clinical investigations, haemodynamic parameters do not make the diagnosis of cirrhosis on their own and should be used in conjunction with the other parameters. (60)

The hepatic-artery data further showed more haemodynamic changes in the HCV patients. The HCV group had an increased mean hepatic artery PSV, RI and PI, while EDV was slightly decreased.

Increased downstream vascular resistance due to intrahepatic remodelling may be the cause of a high RI. In a study by Piscaglia et al. (1997), the RI of the intrahepatic hepatic-artery rose from healthy controls to those with chronic hepatitis and cirrhosis. They also found that there was a correlation between presence and size of oesophageal varices in the cirrhotic patients with RI. The HCV group had a slightly higher mean RI of 0.72, which was also above the proposed threshold of 0.705 by Soker et al. (2016) to differentiate cirrhotic from non-cirrhotic patients with viral hepatitis. These cut-off values, however, should be used with caution since they can differ with population, disease stage, equipment and measurement location.

The first hypothesis test showed that there were statistically significant differences in portal-vein flow velocity, hepatic-artery PSV, RI and PI between the two groups, the HBV group and the HCV group. However, there was no significant difference in hepatic artery EDV. Thus, the null hypothesis was rejected and the alternative hypothesis was accepted. The higher velocity of the hepatic artery in HCV patients might have clinical implication. Park et al. 2017 reported that a high hepatic arterial velocity was significantly correlated with a high MELD score, splenomegaly and ascites in patients with cirrhosis (63). Their study, however, failed to establish common relationships between the severity of disease and RI and portal-vein velocity. This distinction suggests that Doppler parameters do not behave alike in all populations and/or in various stages of chronic liver disease.

A significant negative correlation was found between portal-vein velocity and hepatic-artery PSV, RI and PI in the second hypothesis test. The most significant correlation was portal-vein velocity and hepatic artery RI. These findings were consistent with the portal-arterial interaction hypothesis, where a decrease in portal flow was accompanied by an increase in hepatic arterial velocity and increase in resistance related parameters. The authors of Gülberg et al. (2002) showed that there is still some HABR preserved in advanced cirrhosis (59). Transjugular intrahepatic

portosystemic shunt (TIPS) placement was followed by changes in portal-perfusion, which were correlated to changes in hepatic-artery RI. The role of hepatopetal and hepatoportal flow regulation in cirrhosis was also confirmed by Zipprich et al. (2021) who showed that blockade of the endothelin-A receptor lowers portal pressure and raises hepatoportal flow. There is no significant correlation found between EDV which further indicates that EDV might not be as sensitive as PSV, RI or PI as representing the compensatory haemodynamic changes in this sample.

It is important to note that the degree of alteration seen in HCV patients should not be seen as proof that HCV in general causes more haemodynamic injury than HBV. This study adopted a cross sectional method, unequal group (HBV and HCV) and non-probability sampling. It was also not adjusted for Child-Pugh classification, fibrosis stage or MELD score, nor for antiviral treatment or duration of infection or relevant comorbidities. Doppler results may additionally vary according to the equipment and observer. However, equipment variability in the measurement of hepatic arterial Doppler was greater than interobserver variability, as pointed out by Hübner et al. (2005) (60), which underscores the need for standardised equipment and procedures.

HBV-induced chronic liver disease can also give rise to clinically relevant circulatory changes of the liver. To assess the oesophageal varices in patients with HBV-related cirrhosis, Li et al. (2017) showed that contrast-enhanced ultrasound assessment of hepatic and portal circulation could be helpful (62). Similarly, the decreased EHLF was also associated with disease severity and prognosis in patients with HBV-ACLF (Chen et al., 2021). Thus, any differences between these cohorts (HBV vs. HCV) may be either due to distinct differences in disease severity or clinical characteristics and not solely due to viral type.

The results of this study indicate that Doppler ultrasonography is a feasible and non-invasive technique for assessing hepatic haemodynamic adaptation in chronic viral liver disease, albeit with

certain limitations. Because portal-vein velocity and direction in conjunction, hepatic-artery PSV, hepatic-artery RI and hepatic-artery PI seem to be more informative than a single assessment. If portal velocity is diminished, hepatic arterial indices are elevated, or flow is hepatofugal, more fibrosis work up and/or portal hypertension and hepatic decompensation work up should be performed. For future studies, it is recommended to have larger and well-balanced HBV and HCV cohorts and to adjust for disease severity and treatment status, as well as to employ longitudinal follow-up.

## **Chapter 6**

### **CONCLUSIONS**

Finally, the study found hepatic artery buffer response and Doppler haemodynamics parameters to be different in HBV- and HCV-related CLD. The portal vein flow velocity was lower in HCV patients, portal vein diameter was higher, hepatic artery peak systolic velocity was higher, and portal vein resistive index and pulsatility index were higher in HCV patients. HCV group also had altered hepatic artery buffer response. Results of significant negative correlations between portal vein flow velocity and hepatic artery PSV, RI and PI further supported the physiological concept that the changes in portal venous inflow are followed by compensatory changes in hepatic artery flow. However, there was no significant difference or relationship found for hepatic artery EDV. In general, Doppler ultrasonography was useful, easily available and non-invasive, and was found to be a useful tool to assess portal-arterial haemodynamic changes in chronic viral liver disease. However, the results should be taken with caution due to the small number of centres, and the small numbers of cases and controls studied and the lack of control for disease severity and other clinical parameters.

#### **6.1 Limitation**

- The relatively small sample size of 60 participants may have reduced the statistical power of the study and limited the detection of smaller group differences.

- The study was carried out in one hospital, so the findings may not be applicable to other hospitals and populations.
- Selection bias may have occurred in non-probability sampling because the participants are not necessarily representative of all patients with HBV- or HCV-related chronic liver disease.
- The cross sectional design did not allow for the determination of causality and did not allow for evaluation of changes in HABR over time.
- The statistical estimates may have been imprecise and not directly comparable due to the fact that the number of HBV cases was considerably different from the number of HCV cases.
- Important clinical factors such as fibrosis stage, the severity of cirrhosis, MELD score, Child-Pugh classification, antiviral treatment status and duration of infection were not controlled.
- Despite a standardised scanning protocol, Doppler measurements may have been influenced by the operator's technique, equipment settings, patient fasting and physiological variation.

### 6.2 Recommendations

- Doppler evaluation of both PV Doppler parameters and HA Doppler parameters should be performed as part of the routine assessment of patients with chronic liver disease due to HCV and HBV.
- The portal vein velocity, hepatic artery PSV, RI and PI should be used together, as a combination of parameters may be more suitable to indicate the hepatic artery buffer response than a single parameter.
- Hepatofugal flow and/or portal vein velocity reduction, or hepatic artery resistance increase, should prompt subsequent evaluation for portal hypertension, fibrosis and hepatic decompensation.
- A larger and more balanced number of HBV and HCV patients needs to be studied in the future to make better comparisons between the two groups.
- Multicentre studies are needed to

enhance the generalisability of results to different hospitals, geographic areas and patient groups.

- Future studies should differentiate participants based on fibrosis stage, Child-Pugh class, MELD score and length of viral infection to assess the impact of disease severity on HABR.
- Before and after antiviral treatment, the changes in hepatic haemodynamics should be assessed by longitudinal studies to evaluate whether or not successful antiviral treatment improves portal and hepatic arterial blood flow.

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